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PROCEEDINGS

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CONTENTS

PAGE.

BIOGRAPHY OF FREDERIC SCHILLER LEE,
Fourth president of the Society for Experimental Biology and Medicine v

SCIENTIFIC PROCEEDINGS (35th–39th meetings):
Communications of the thirty fifth meeting, October 20, 1909. . 1
Communications of the thirty sixth meeting, December 15, 1909. . 21
Communications of the thirty seventh meeting, February 16, 1910. 61
Communications of the thirty eighth meeting, April 20, 1910. . 87
Communications of the thirty ninth meeting, May 18, 1910. . . 135
Recapitulation of the names of the authors and of the titles of the communications 181

EXECUTIVE PROCEEDINGS (35th–39th meetings) 193
REGISTER OF NAMES AND ADDRESSES OF THE MEMBERS . . . 195
LIST OF OFFICERS 201
CLASSIFIED LIST OF MEMBERS. 203
INDEX OF THE SCIENTIFIC PROCEEDINGS. 207

MUSEUM BASILEENSE
NATURAE HISTORIAE

Frederic S. Lee.

FREDERIC SCHILLER LEE.

Fourth president (1908–10) of the Society for Experimental Biology and Medicine.[1]

Frederic Schiller Lee was born at Canton, New York, June 16, 1859. His ancestors, of vigorous English stock, came early to Massachusetts, and they and their children played active and honorable parts in the making of the New England colonies. In his boyhood a love of nature was developed in him, and a scientific career was foreshadowed early. From the first he lived in an academic atmosphere. He received his college training at St. Lawrence University, of which his father had been president, and obtained his A.B. in 1878. After a few years of scientific teaching, he became one of the band of young men who felt the stimulus of the newly created Johns Hopkins University, and at that institution had his first adequate opportunity of gratifying his ambition for the best scientific training. The four years from 1881 to 1885 he spent at Johns Hopkins under Newell Martin and William Keith Brooks, and was successively assistant, graduate scholar and fellow in biology. He received his doctorate in philosophy there in 1885. During the following year he engaged in physiological research at Leipsic with Carl Ludwig and von Frey. On returning to this country he taught physiology for one year at St. Lawrence University and for four years at Bryn Mawr College, and in 1891 he was called to Columbia as demonstrator of physiology. In 1895 he became an adjunct-professor, and since 1904 he has been a professor of physiology.

Professor Lee entered upon the study of physiology from the standpoint of general biology, and this fact has influenced his whole subsequent career. He has consistently viewed physiology as primarily a biological science. While rigidly insisting upon a large knowledge of it as the indispensable condition of scientific medicine, as a university study he has deprecated its almost exclusive development in medical schools, and has constantly urged its inclusion also among the scientific courses of the university.

[1] Similar brief biographies of former presidents appear in Vols. II, III and V.

He was instrumental in opening the department of physiology at Columbia to post-graduate students in the School of Pure Science, an example which was soon followed by other medical departments, and he was one of the first in this country to offer courses in general physiology.

His contributions to science have also been mainly in the field of general physiology. During his student life he investigated the action of intermittent pressure, defibrinated blood and certain salts, upon the tone of arteries; and his doctor's dissertation was on the subject of arterial tonicity. At Leipsic he investigated the electrical phenomena of contracting muscle, and showed for the first time that there exists a close parallelism between the electrical and the mechanical phenomena. The former continue nearly or quite throughout the latter, and like the latter are extended and diminished in fatigue. Professor Lee spent several summers at the Marine Biological Laboratory at Woods Holl, and there made the most exact and detailed study that has yet been made of the rôle of the parts of the ear in the maintenance of bodily equilibrium, correlating the results with observations on the nerves of the lateral line, and studying the hearing of fishes. He has examined experimentally the theory of the phototactic response, and has shown that the distinction hitherto made between the response of organisms to the intensity of light and their response to the direction of its rays, is not justified. The phototactic response is conditioned by the intensity of light and the distinction between phototaxis and photopathy, as different forms of irritability, is unwarranted. He has studied the action of alcohol on muscle and has emphasized the fact that in small quantities alcohol is capable of increasing the working power of that tissue. He has studied the phenomena of rigor mortis and the survival of mammalian muscle after somatic death. By the use of very exact experimental methods he has contributed to our knowledge of the phenomena of normal and pathological fatigue and their causes. He has explained the treppe of muscle as being due to the augmenting action of small quantities of certain metabolic products, such as carbon dioxide and lactic acid, the same substances which in larger quantities are depressing or fatiguing to muscle. He ascribes the phenomenon of the summation of stimuli to the same substances, which are produced even

during the course of subminimal stimulation. He has investigated the variations in the irritability of muscle under various conditions. In these various ways he has thrown light upon many of the general and fundamental phenomena of protoplasmic action.

Besides contributing to "An American Text-book of Physiology," "The Harvey Lectures," "A History of Columbia University," and other books, Professor Lee has translated and edited Verworn's "Allgemeine Physiologie," a work which has proved of value in enlarging the scope of physiological conceptions. He has revised and edited Huxley's historic "Lessons in Elementary Physiology." He has been a member of the editorial board of the *American Journal of Physiology* since its beginning. For several years he has been one of the scientific directors of the New York Botanical Garden. Besides being a member and for two years the president of the Society for Experimental Biology and Medicine, he is a member of the American Society of Naturalists, the American Physiological Society, the Harvey Society and other scientific societies, an associate fellow of the New York Academy of Medicine, and a fellow of the American Ethnological Society, the American Association for the Advancement of Science and the New York Academy of Sciences. In these societies he has held various positions of honor.

SCIENTIFIC PROCEEDINGS.

Abstracts of the Communications.

Thirty fifth meeting.

College of Physicians and Surgeons, Columbia University. October 20, 1908. President Lee in the chair.

1 (411)

The influence of alcohol and other anesthetics on developing embryos.

By **Charles R. Stockard.**

[*From the Laboratory of Embryology and Experimental Morphology, Cornell Medical College, New York City.*]

In previous experiments I had found magnesium salts to induce peculiar defects in the eyes of fish embryos. When eggs are subjected to such solutions, a large percentage of the embryos present all degrees of the cyclopean defect, while other individuals develop a normal eye on one side of the head with its mate on the other side small and defective or entirely absent. This latter condition was termed *Monophthalmicum asymmetricum* to distinguish it from true median cyclopia.

It seemed probable that these defects were due to the anesthetic properties of the magnesium solutions and to test this supposition eggs have been treated with several other anesthetics; alcohol, chloroton, chloroform and magnesium again. All of these act particularly upon the developing central nervous system and sense organs. Other parts of the body are somewhat delayed in their rates of development but are normal in appearance.

Alcohol gave the most decided and interesting results. When used in certain strengths it causes from 90 to 98 per cent. of the embryos to show typical defects in the head region. The eyes are either cyclopean, asymmetrically monophthalmic, both small, poorly formed and deeply buried in the head or entirely absent.

The ears are normal in many individuals but not infrequently both are poorly developed and often one is scarcely formed. When one eye is large and the other small or absent the well formed ear is usually on the side with the more perfect eye. The general growth rate is retarded and spina-bifida sometimes occurs.

Chloroton, chloroform and ether are more general in their anesthetic effects, the entire embryo being unusually depressed. In all of these substances, however, if the concentration be delicately regulated the eye defects so common in alcohol and magnesium may be produced.

Cyclopia and other eye defects, in fish embryos at least, are produced by lessening the developmental energy at certain critical stages. This is readily accomplished by treating the developing embryo with anesthetics.

2 (412)

On the variation in the resistance of human erythrocytes in disease to hemolysins, with especial reference to syphilis.

By **RICHARD WEIL.**

[*From the Department of Experimental Therapeutics, Cornell University Medical School.*]

The observations herein presented have to do with the alterations in the reaction of the red blood cells to the action of certain hemolytic agents. This alteration in the resisting power of the red cells may be either in the direction of a diminution or an increase in their resistance; increased resistance, however, is apparently a much more striking and demonstrable feature than is the reverse, and seems to me, furthermore, to be of considerable importance from the standpoint of immunity. My observations comprise a study of almost five hundred human cases, normal and diseased, in which the red cells were subjected to the action of various lytic agents. Among the agents so studied were various acids and alkalies; certain metallic salts, such as bichloride of mercury, which possesses a well-known hemolytic power; certain vegetable hemolysins, such as saponin, digitonin and cyclamin, and certain animal venoms, such as rattlesnake and cobra venom. The results obtained from the study of the inorganic lysins have not been such that they could be reduced to a definite correlation with any given

class of corpuscles studied. The results with the organic lysins were of greater interest, the most marked feature being the striking resistance offered by the corpuscles derived from certain cases of syphilis to the action of saponin and allied poisons. On the other hand, not all of the cases with syphilis manifested this result; indeed some of them seemed among the least resistant of the bloods which were studied. Further analysis revealed the fact that some cases of advanced tuberculosis of the lungs also possessed corpuscles marked by resistance to these poisons, although their resistance did not equal that of the cases of syphilis. Added to these unsatisfactory conditions was the fact that the technique, unless most rigidly observed, failed to demonstrate these differences satisfactorily.

Digitonin proved a far more satisfactory glucoside than saponin, inasmuch as it separated far more cases of lues from the non-luetic than did saponin, but it shared the disadvantages already outlined, namely, the extreme delicacy of the reaction, which left too little margin of difference between the luetic and the non-luetic cases and the extreme care necessary in the technique, inasmuch as the slightest difference in the handling of the various specimens of erythrocytes sufficed to invalidate the result.

In looking for some other hemolysin of the same nature, I was guided by the fact that the sapotoxins previously investigated act upon the red cells through their content in cholesterin and in lecithin. H. Sachs states that cobra venom is an indicator of the lecithin content of red cells; I therefore made a further study of snake venom, using rattlesnake venom and cobra venom. Of the rattlesnake venom I had two specimens, one of which I owe to the kindness of Professor McFarland, of Philadelphia; neither has given me satisfaction, although I am not ready to make a final report on the subject. I have also had two samples of cobra venom for one of which I am indebted to Dr. Flexner. Cobra venom has fulfilled my expectations even more completely than I had hoped. I have tested approximately 150 cases of human blood, of which 50 were from syphilitics, and I believe that it is justifiable to make a preliminary statement of the results of these tests. To summarize the results in brief: luetic conditions are characterized by their resistance to cobra venom. This group comprises also some

fairly early cases of lues. The reaction does not invariably determine luetic conditions, but is marked in about 90 per cent. of the cases. I have had my reactions controlled in every case, not only by the clinical history and findings, but by the results of a Wasserman test done in every case on the serum either by Dr. Kaplan, of the Montefiore Home Laboratory, or by Dr. Warren, of the Cornell Laboratory — to whom I am indebted for these data. In comparing our results, it is a very striking fact that I have obtained fewer positive reactions in the case of the so-called parasyphilitic diseases — namely, tabes dorsalis and general paresis. The cause of this discrepancy I am unable to determine. It is possible that it might disappear in a larger series of cases; it is possible that when lues attacks the lipoids of the central nervous system, it spares those of the red cells; finally, it is possible that tabes and general paresis give a greater number of positive Wasserman reactions than corresponds to the proportion of luetic infection among these cases. I have also failed to get a positive reaction in three cases of scarlet fever, and in two cases of polycythemia, and in one case of scleroderma, in all of which the Wasserman reaction was positive, but inasmuch as the positive Wasserman reaction in these cases is to be regarded as probably due to a source of unavoidable error resident in the nature of the reaction, I believe that the cobra venom has proven a superior reagent in these cases. In certain types of cases, the method which I have described has a distinct advantage over the Wasserman reaction. In the first place, it is applicable to cases with jaundice; in the second, it is positive for some time after mercurial treatment has abolished the Wasserman reaction; and finally, it is positive in a very large percentage of very old, quiescent cases in which Wasserman reaction is negative. The cases which most closely approach the luetics in point of resistance are some cases of tuberculosis, but they have not as yet proven a source of confusion. In the very early florid cases of lues, with chancre and the first rash, the resistance of the corpuscles to cobra venom is regularly diminished considerably below the normal.

As regards the theory involved in this reaction, I am unable to advance a very satisfactory explanation. I presume that the well-known relationship of lecithin to the Wasserman reaction,

and to the action of cobra venom will play a rôle in the final solution, but my own experiments have not hitherto thrown any light on the subject.

As regards the method, the blood is to be drawn into 2 per cent. sodium citrate, thoroughly washed, and made up into a 4 per cent. suspension in 0.9 per cent. common salt. The suspensions may be tested at once, or may be kept in the ice box until the following day and then tested. Equal quantities of a 1 : 8,000, and of a 1 : 15,000 dilution of cobra venom are then added, and after one hour incubation the results may be read. If still higher dilutions, as from 10,000 to 60,000 are used, the cells must be incubated for one hour and observed the next morning, but nothing is gained by this except more delicate gradations. Syphilitic cells should resist a solution twice as strong (1 : 8,000) as that which is sufficient to destroy all the control (1 : 15,000). If intermediate solutions are also used, it is possible to trace the gradual loss of the reaction in treated cases. It is probable that each specimen of cobra venom would have to be independently standardized, but one gram would then suffice for about 5,000 tests.

3 (413)

The distribution of sulphur compounds in brain tissue.

By **W. KOCH** and **F. W. UPSON.**

[*From the Hull Physiological Laboratory of the University of Chicago.*]

The distribution of sulphur expressed in per cent. of total among the various chemical groups of the whole brain is approximately as follows: (1) Proteins, 60 per cent.; (2) lipoids, 26 per cent.; (3) water, soluble extractions or neutral sulphur compounds, 9 per cent.; (4) sulphates, 5 per cent. (Total sulphur in per cent. of dry matter is from 0.45 to 0.5.)

Sulphur occurs in the following five stages of oxydation: (1) Cystein R—S—H, (2) cystin R—S—S—R, (3) sulphonate or taurin-like R—SO_2—OH, (4) ethereal $(RO)_2SO_2$, (5) sulphates.

Taking the various groups of chemical constituents, the following stages of oxydation of sulphur have been found in each: Protein — (1) cystein, (2) cystin, (3) ethereal; lipoids — (4) ethereal. Water soluble extractives (1 or 2 or both) most likely cystein, (3) sulphonate or taurin-like.

The present investigation has concerned itself mainly with the water soluble extractive form of sulphur, which besides containing a compound which is either taurin or an immediate precursor of taurin, contains another group of compounds which appear to bear a close resemblance to the group of neutral sulphur compounds found in the urine. In view of the fact that Folin considers the neutral sulphur of the urine as a measure of tissue metabolism, this observation becomes of special significance. The possibility of comparing the metabolic activity of different tissues with one another, and of the same tissue under different conditions, is at once apparent.

No very close resemblance can be demonstrated until we know the chemical structure of these compounds.

The resemblances so far found are as follows: The neutral sulphur compounds of the tissues and of the urine are both soluble in water, soluble in dilute alcohol, not precipitated by phosphotungstic or tannic acids, precipitated by mercuric acetate. They do not precipitate with barium chloride direct or after boiling with hydrochloric acid. They contain lead blackening sulphur.

4 (414)

The study of autolysis by physico-chemical methods.

By **ROBERT L. BENSON** and **H. GIDEON WELLS.**

Further studies of autolytic changes in animal tissues by means of the depression of the freezing point and rise in conductivity show the great value of these methods of estimating the rate and progress of autolysis. The results obtained in this way give a much more accurate and valuable indication of autolytic changes in any given tissue than the commonly used determination of the percentage of nitrogen in coagulable form. Autolysis comprises the disintegration of the cell components and involves a great many substances, some of which are coagulable proteins and many of which are not. If we determine the proportion of nitrogen that is made non-coagulable by heat, we get a figure which is the same whether the coagulable nitrogen that has been made incoagulable is in the form of proteoses and peptones, or has been carried to the ultimate amino-acids or even further. The several steps that take place in the autolysis of nucleins also have no effect on this figure after the

first splitting out and rendering soluble of the nucleic acid complex. Only the autolytic changes which affect coagulable or insoluble nitrogenous cellular constituents are shown, and the changes in such substances as collagen or the other non-coagulable nitrogenous tissue elements are not brought out. In other words, the ratio of coagulable and non-coagulable nitrogen in autolyzing tissues shows only one of the many changes that are being accomplished by the autolytic processes.

On the other hand the freezing point determination gives an absolute, delicate and reliable measure of the disintegration of the tissue, since practically every step of this disintegration results in an increase in the number of molecules in the solution. A freezing point curve is, therefore, a correct picture of the total disintegrative change that is taking place in the mixture, which a non-coagulable nitrogen curve cannot well be. If we supplement the freezing point curve with a conductivity curve we secure, in addition, information as to qualitative changes, for the conductivity curve indicates only the increase in the number of free ions, which we know are largely supplied by certain of the products of autolysis, while the difference between the two curves gives us a measure of the newly formed non-electrolytes. The information obtained by these two methods is, therefore, much more instructive as to the actual amount and rate of autolytic change than are the results of coagulable nitrogen estimations, and in addition the methods involved are much simpler and easier. A score of freezing point determinations and a hundred conductivity measurements can be obtained with no more expenditure of time and labor than one nitrogen determination, and much smaller quantities of material suffice — a point of great importance in many investigations.

As a general rule the curves of conductivity increase and freezing point depressions for the same tissue parallel each other fairly closely; at first the change in conductivity proceeds slower than the change in freezing point, but later the conductivity continues to rise when the depression of freezing point has come nearly to a standstill. This last phenomenon probably depends upon the liberation of ammonia from the amino-acids and purines by the amidases, and the formation of organic acids. Blood serum, lymph and cerebro-spinal fluid show no evidence of autolysis by

physical methods, but the conductivity of blood slowly falls as the hemoglobin is liberated from the corpuscles. The inhibiting effect of blood serum upon autolysis seems to be less readily destroyed by heat than is usually estimated.

5 (415)

The influence of adrenalin in phlorhizin diabetes.

By **A. I. RINGER.** (By invitation.)

[*From the Physiological Laboratory of the New York University and Bellevue Hospital Medical College.*]

These experiments were performed with the object of ascertaining whether or not the contention of Blum as well as of Eppinger, Falta and Rudinger, that adrenalin stimulates the conversion of fat into dextrose, is well founded. On careful analysis of their data, one may find every reason to believe that the animals used for their adrenalin experiments were not glycogen free, and that the extra sugar eliminated after the administration of adrenalin did not come from the ingested fat, but from glycogen or from the sugar of the blood.

If a phlorhizinized animal be exposed to cold and rendered glycogen free, any intraperitoneal injection of adrenalin ought to be followed by an extra elimination of sugar and a rise in the D : N ratio, provided the theory of the conversion of fat into carbohydrate is true. That this is not the case will be seen from the accompanying protocols.

DOG NO. 5.

March 6, 1909.	Dog fasting.
March 7, 1909.	Dog fasting.
March 8, 1909.	2 gm. of phlorhizin injected at 8 A. M., 3:30 P. M. and 10 P. M.
March 9, 1909.	2 gm. of phlorhizin injected at 8 A. M., 3:30 P. M. and 10 P. M. At 5:15 P. M. the dog was given a bath at a temperature of 8° C. for 30 minutes and while wet was placed in a cold room for 5½ hours.
March 10, 1909, 9:30 A. M.	2 gm. phlorhizin injected subcutaneously.
March 10, 1909, 10:30 A. M.	Catheterized and bladder washed. Weight of dog 9.12 kg.

TABLE I.

Time.	No. of Hrs.	Total N.	N per Hour.	Total D.	D per Hour.	D : N.
10:15 A. M.–						
1:15 P. M.	3	1.57	0.523	5.168	1.723	3:29
1:15 P. M.		0.009 gm. of adrenalin injected intraperitoneally.				
1:15 P. M.–						
8:45 A. M.[1]	19½	8.073	0.414	25.928	1.33	3:21

This animal was kept in a cold room for five and a half hours following a period of four days' starvation, inclusive of two days of phlorhizin diabetes. This apparently rendered the animal glycogen free. Administration of adrenalin produced no increase in the elimination of sugar and no change in the D : N ratio.

DOG NO. 7.

April 10, 1909. Dog fed last.

April 11, 1909. Dog starving.

April 12, 1909. Dog starving.

April 13, 1909. Dog starving. 2 gm. of phlorhizin injected subcutaneously at 8:50 A. M., at 4 P. M. and 11 P. M.

April 14, 1909. Dog starving. 2 gm. of phlorhizin injected subcutaneously at 8:50 A. M., at 4 P. M. and 11 P. M. At 5 P. M. dog given a cold bath at a temperature of 5° C. for 30 minutes, and while wet placed in cold room for the night.

April 15, 1909. 8:50 A. M. 2 gm. of phlorhizin injected subcutaneously.

April 15, 1909. 10:25 A. M. catheterized and bladder washed. Dog's weight, 8.76 kg.

TABLE II.

Time.	No. of Hrs.	Period.	Condition.	Total N.	N. per Hour.	Total D.	D. per Hour.	D : N.	Remarks.
April 15, 1909.									
10:25 A.M.–3:25 P.M.	5:00	I.	Phlorhizin.	2.264	0.453	7.248	1.449	3.2	
3:25 P. M.–8:25 A. M.	17:00	II.	Adrenalin and phlorhizin.	6.297	0.37	30.176	1.775	4.79	At 3:25 P. M. 0.005 gm. of adrenalin injected intraperitoneally.
April 16, 1909.									
8:25 A. M.–3:40 P. M.	7:15	III.	Phlorhizin.	2.973	0.41	9.376	1.29	3.12	
3:40 P. M.–8:40 P. M.	17:00	IV.	Adrenalin and phlorhizin.	7.129	0.419	23.92	1.407	3.35	At 3:40 P. M. 0.005 gm. of adrenalin injected intraperitoneally.

Throughout the course of the experiment the phlorhizin was injected regularly at 8:00 A. M., 3:45 P. M. and 11:55 P. M.

[1] At 4:10 P. M. and 10:45 P. M. 2 gm. of phlorhizin were injected subcutaneously.

TABLE II. — *Continued.*

Time.	No. of Hrs.	Period.	Condition.	Total N.	N. per Hour.	Total D.	D. per Hour.	D : N.	Remarks.
April 17, 1909.									
8:40 A. M.–3:40 P. M.	7:00	V.	Phlorhizin.	2.973	0.426	9.264	1.323	3.116	
3:40 P. M.–8:40 A. M.	17:00	VI.	Adrenalin and phlorhizin.	6.687	0.393	21.824	1.28	3.26	At 3:40 P. M. injected 0.005 gm. of adrenalin.
April 19, 1909.			Death of dog.						

This animal was treated in a similar manner to Dog No. 5, but, because the April night was not as cold as the night of March, the dog was not sufficiently chilled to exhaust it of all its glycogen. The first administration of adrenalin was therefore followed by a rise in the D : N ratio, showing that a sweeping out of the carbohydrates of the tissues took place. The second and third administration of adrenalin, however, failed to produce any extra sugar elimination.

These experiments show very clearly that adrenalin has not the power of converting fat into dextrose.

6 (416)

A method for the determination of small quantities of iodine in organic material.

By **ANDREW HUNTER.**

[*From the Department of Physiology, Biochemistry and Pharmacology, Cornell University Medical College, Ithaca.*]

The estimation of iodine in thyroid gland and similar material is usually carried out by the method of Baumann or one or other of its various modifications. All varieties of the method have for their basal operation the quantitative conversion of the organically combined iodine into hydriodic acid. For the investigation reported by Simpson and myself I have worked out a method which rests upon a different principle altogether.

By a procedure which involves, first, the oxidation of the material with a mixture of saltpeter and potassium sodium carbonate, and, second, the action of an excess of chlorine upon the

acidified solution of the product, the iodine occurring in animal tissues may be quantitatively converted into iodic acid. After the excess chlorine has been removed, addition of potassium iodide leads to the liberation of exactly six times the original amount of iodine. The iodine thus set free may be titrated directly with a sodium thiosulphate solution of suitable strength. It is claimed for the method that it excels the various forms of the Baumann method, not only in cleanliness, convenience, and rapidity, but also in accuracy. Details will be published as soon as a larger series of control analyses is completed.

7 (417)

Relations between the thyroid and pituitary glands.

By **Sutherland Simpson** and **Andrew Hunter.**

[*From the Department of Physiology, Biochemistry and Pharmacology of the Cornell University Medical College, Ithaca, N. Y.*]

Recent work by Herring[1] has shown that complete removal of the thyroid in rabbits, cats and dogs is followed by definite histological changes in the pituitary body. A greatly increased production of colloid material by the cells of the pars intermedia was indicated. Accumulations of colloid were observed in the nervous portion of the posterior lobe and in the laminæ forming the floor of the third ventricle whence it appeared to find its way between the ependyma cells into the infundibular recess and brain ventricles.

It is believed by many that the iodine-containing substance — the so-called iodothyrin or thyroiodin — is the active substance of the thyroid gland. Reid Hunt states that the physiological activity of the thyroid varies directly with the percentage of iodine which it contains. According to Baumann, Halliburton[2] and others the pituitary yields no iodine. Gideon Wells,[3] from an analysis of fourteen normal human pituitaries, found an average amount of 0.0036 milligram of iodine for each gland — about one fiftieth of the quantity found in the thyroid. Ox pituitary obtained from Armour and Co. tested by Hunter's method gave no

[1] *Quart. Jour. of Exper. Physiol.*, 1908, i, 281.

[2] *Quart. Jour. of Exper. Physiol.*, 1909, ii, 229.

[3] *Jour. of the American Med. Assoc.*, 1897, xxix, 897, 954, 1007.

iodine and sheep's pituitary from the Ithaca slaughter house yielded only a trace.

Our experiment was performed at the suggestion of Professor Schäfer with the view of determining whether iodine appears in the pituitary after thyroidectomy. We removed the thyroid glands completely from ten sheep. Each was weighed at the time of removal and again when dried, and the iodine estimated. Great variation was found in the ratio of thyroid to body weight in different individuals, but the iodine corresponded pretty closely to the weight of the gland.

Five of the sheep were infected by a parasite and died at intervals of from six to thirty-two days after the operation. The remaining five showed no symptoms and were killed from forty-seven to fifty-six days after throidectomy. After death the pituitary was removed, weighed, dried and put aside until all had been collected and then on account of the small size of the individual glands, they were examined for iodine collectively by Hunter's method. None was found. The weight of the substance available for examination was 1.02 grams. In this amount 0.005 milligram could have been detected with certainty.

8 (418)

Parabiosis as a test for circulating antibodies in cancer.

By **PEYTON ROUS.**

[*From the Laboratories of the Rockefeller Institute for Medical Research, New York.*]

Sauerbruch and Heyde have united animals side by side, with an opening between the peritoneal cavities and suture of the apposed skin and connective tissue. They find that healing between two individuals thus joined brings with it a considerable physiological intimacy. Ranzi and Ehrlich, following them, have demonstrated that circulating antibodies pass with ease from one of such a pair to the other. On this evidence it seems possible to utilize the condition (parabiosis) for experiments on the question of the existence or non-existence of circulating antibodies for cancer. Accordingly, I have united white rats with a growing tumor, the result of transplantation, to others which had proved themselves resistant to the same type of neoplasm. Careful watch

was kept for signs of retarded development or retrogression in the tumors thus brought under the continued influence of blood from a resistant animal, but no alteration of the sort was observed. The growths extended with the same rapidity as those in control animals. The findings are against the presence in circulation of destructive antibodies for cancer.

The Flexner-Jobling adeno-carcinoma was the tumor employed. Animals were selected which bore in the subcutaneous tissue of one side a vigorous growth 1 to 3 centimeters in diameter. Some were kept as controls and others placed in parabiosis with resistant rats. These latter had failed on three successive implantations to develop a tumor. The appearance in most of them of a small retrogressing nodule after the first implantation, and the complete absence of such a nodule after the later ones pointed to an acquired immunity in addition to the natural resistance. Experiments with rats of high acquired immunity are now under way.

Sauerbruch and Heyde found that for the healing together of rabbits or dogs it is imperative that they be young and of the same litter. Even then they did not endure the union for more than two weeks, one succumbing within that time to a cachexia, incident, it is supposed, to the new metabolic relation. My observations show that white rats tolerate much better the conditions of union. Adult animals of different litters will heal together *per primum* and live in parabiosis as long as thirty-four days. Evidently those tissue distinctions between individuals based on parentage and age are much less marked in white rats than in some other species.

9 (419)

The excretion of calcium and magnesium after parathyroidectomy.

By **JEAN V. COOKE.** (By invitation.)

[*From the Carnegie Laboratory, University and Bellevue Hospital Medical College.*]

The brains of dogs dying with parathyroid tetany contain a slightly greater amount of calcium than do those of normal dogs, which would indicate that a decreased calcium content of the brain is not constant in tetany. The magnesium content of the brain is

practically the same in both normal and tetany dogs. The calcium and magnesium content of the feces of normal and parathyroidectomized dogs is similar. During fasting, the excretion of both metals is diminished. The excretion of magnesium, in the urine, in dogs on a constant diet, as well as in those fasting, runs parallel with that of calcium. The excretion of both metals is markedly diminished during fasting. After parathyroidectomy with the animal fasting, the elimination of magnesium is greatly increased, while that of calcium remains unchanged. The augmentation of the magnesium begins before tetany is observed. This increased elimination of magnesium indicates that although there is a disturbance of inorganic equilibrium, it is not limited to calcium. It is suggested that the tetany represents a condition of altered salt equilibrium in the nerve cells brought about by a disturbance in the catalytic processes of the body which increases the acid factors.

10 (420)

Non-fixation of complement.

By **HIDEYO NOGUCHI.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

With a view of obtaining an antihuman hemolytic amboceptor on a large scale, I immunized a goat with thoroughly washed human corpuscles. I obtained a serum of a titre of 0.01 cubic centimeter, that is, capable of complete hemolysis with 1 cubic centimeter of a one per cent. suspension of washed human corpuscles in the presence of 0.01 cubic centimeter of normal goat's or guinea-pig's serum. The reactivating property of normal goat's serum for this ambocepter was found to be somewhat superior to that of guinea-pig's complement. As it would be of great economical value for complement fixation tests to utilize an amboceptor and complement from such a large animal as a goat, instead of using an amboceptor from rabbits and complement from guinea-pigs, I tested the amboceptor and complement from goats as to the possibility of using them in complement fixation tests in general. *It was soon found that no complement-fixation phenomenon can be obtained by using them (antihuman amboceptor from this im-*

mune goat and complement from a normal goat) in connection with the following antigen-antibody combinations: (1) meningococcus-anti-meningococcus serum of Flexner (horse), (2) human-antihuman serum (rabbit), (3) egg-albumen-antiegg-albumen (rabbit), and finally (4) "syphilitic antigen" — syphilitic serum (or Wassermann reaction). With the combinations of (1), (2) and (3), precipitates were first produced, then washed in saline solution by centrifugation, and finally, before use were resuspended in saline solution. That these different precipitates as well as the syphilitic serum with "syphilitic antigen" were not inactive was easily demonstrated by using another hemolytic system. Thus, when the antihuman amboceptor derived from rabbit and complement from guinea-pig or even from goat were used there was complete fixation in each instance. *Again, it was subsequently found that when the antihuman amboceptor derived from this goat is added to these tubes in which complete fixation is beautifully shown by the use of the antihuman amboceptor from rabbits, hemolysis ensues.* There is in such cases retardation in the hemolytic process, but it finally becomes complete. It suggests strongly that these complements are readily fixed by these precipitates or by syphilitic serum and lipoids and remain there inactive in the presence of the amboceptor derived from rabbit, while they become once more detached when the amboceptor from goat is introduced. It is difficult, however, to exclude another possibility, namely, that these sera contain one fixable and one non-fixable set of complements. The former set alone is in action when the amboceptor from rabbits is used, thus explaining the absence of hemolysis in this instance; while the latter set is in operation with the other amboceptor (goat), and, therefore, no fixation phenomenon can occur here. Whether this peculiarity is common to the antihuman amboceptor derived from all goats or simply an exception with this goat, I am unable to answer.

The foregoing observations warn one against an indiscriminate generalization of the Bordet-Gengou fixation phenomenon and require one to adopt that hemolytic system which is experimentally proven to be suitable for demonstrating the fixation of complement. The reactivating faculty of a complement has no bearing on its fixation by the antigen-antibody combinations.

11 (421)

The fate of so-called syphilitic antibody in the precipitin reaction.

By HIDEYO NOGUCHI.

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

The Wassermann reaction for syphilis is also present in the majority of cases of leprosy and it is impossible to distinguish syphilitic and leprous sera by this test alone. With a view of obtaining specific antisera capable of neutralizing the active principles of syphilitic and leprous sera *electively*, rabbits were immunized with syphilitic and leprous sera, each giving positive Wassermann phenomenon. Two more rabbits were injected with normal and negative sera for controls. After several injections given intravenously, these rabbits yielded the antisera, all energetically precipitating for human serum. Before testing whether the antiserum prepared by injecting syphilitic serum exerts a *specific* neutralizing effect on the fixing property of that serum only, it was necessary first to determine the complement-fixing capacity of the precipitate formed by a normal serum and its antiserum. It was found that the entire bulk of precipitate formed by mixing 0.1 cubic centimeter of normal serum and 0.02 cubic centimeter of its antiserum can fix 0.05 cubic centimeter of guinea-pig's complement (using my antihuman hemolytic system), but is unable to prevent hemolysis when 0.07 cubic centimeter of complement is used. The precipitates formed by mixing syphilitic or leprous serum with their corresponding antisera or the antiserum for normal serum were also able to fix guinea-pig's complement in about the same degree as in the instance given above. I next proceeded to investigate whether the anti-syphilitic serum inhibits the occurrence of the Wassermann reaction when added to a strongly positive syphilitic serum. I selected four different syphilitic sera, each capable of fixing 0.1 cubic centimeter of guinea-pig's complement in doses of from 0.003 to 0.005 cubic centimeter by using inactivated sera. To 0.1 cubic centimeter of each serum was added 0.02 cubic centimeter of the anti-syphilitic serum and a precipitate was formed. After one hour's incubation at 37° C.,

0.1 cubic centimeter of guinea-pig's serum was added. To a second tube similarly prepared, besides complement, "syphilitic antigen" was added at the same time. In a third tube, 0.02 cubic centimeter of syphilitic serum, 0.1 cubic centimeter of complement and "syphilitic antigen" were put together. A fourth tube similar to the third but without "antigen" was also prepared as control. These were incubated for one hour at 37° C. and then one cubic centimeter of a one per cent. suspension of washed human corpuscles and two units of anti-human amboceptor (rabbit) were put into each tube. After further incubation hemolysis was observed in all but the third tube. A further analysis revealed that the precipitate formed by syphilitic sera and anti-syphilitic serum fixes the same amount of complement as that by a normal precipitate, *but the complement-binding property of the syphilitic serum in the presence of "syphilitic antigen" disappears after precipitin reaction takes place.* This phenomenon was found to be non-specific, as the antiserum for normal or leprous serum also caused a similar phenomenon. A positive reacting leprous serum could be made negative by any of the antisera in the same manner. No differentiation could, therefore, be made by the use of specific antisera between syphilitic and leprous sera both giving positive Wassermann reactions.

There is a close relation between the precipitin reaction and the disappearance of the Wassermann reaction in syphilitic and leprous sera. A precipitin-containing serum for human serum should not be employed as amboceptor in doing the Wassermann reaction by my system. To insure against this danger, the amboceptor should be produced by injecting rabbits with thoroughly washed human corpuscles.

12 (422)

The energy metabolism of parturient women.

By **THORNE M. CARPENTER** and **JOHN R. MURLIN**.

[*From the Nutrition Laboratory of the Carnegie Institution of Washington, Boston, Mass.*]

Experiments designed to compare the energy metabolism of mother and child just previous to and immediately following parturition were carried out with the bed calorimeter. Three subjects

were secured through the out-patient department of the McLean Lying-in Hospital. They were cared for in the New England Deaconess Hospital near the laboratory and were kept on a carefully regulated diet, which, except for the day of parturition and one or two days thereafter, was essentially the same throughout for each case. Early in the morning before breakfast was taken, the subjects were brought to the laboratory (in an ambulance when necessary) and were placed in the calorimeter for periods of two or three hours during which hourly determinations of the carbon dioxide output, the oxygen absorption, the heat elimination and the heat production were made.

The heat production was calculated also by the Zuntz method from the amount of nitrogen in the urine, the carbon in the expired air and the oxygen absorbed. A very satisfactory agreement was found between the two methods.

Two of the subjects were primiparæ and one was a multipara. In both primiparæ, the heat production of mother and child was found to be slightly larger just previous to parturition than it was after the temperature had returned to normal following parturition. In the multipara, it was slightly higher following parturition than before. The results, therefore, are in sharp contrast with results obtained by one of us[1] on the dog where the heat production as calculated from the excreta was very much greater following birth of the young.

The heat production of the mother alone was obtained by direct determination and that of the child by difference. The three cases agreed in showing a heat production per kilogram per hour for the child approximately two and a half times that of the mother under the same conditions.

[1] *Proceedings of the American Physiological Society*, 1909, xxiii, 32.

13 (423)

The relation between ciliary and muscular movements.

By **Alfred G. Mayer.**

[*Performed at the Marine Laboratory of the Carnegie Institution at Tortugas, Florida.*]

It appears that in scyphomedusæ the nervous stimulus which produces each pulsation is caused by the constant formation of a uric oxalate of sodium in the marginal sense-clubs. This sodium oxalate precipitates the calcium which constantly enters the sense-club from the surrounding sea-water, and forms crystals of calcium oxalate, while sodium chloride is set free. Thus the stimulus which produces pulsation is due to ionic sodium. Pulsation cannot be maintained by the sense organs unless calcium constantly enters them to form the calcium oxalate, and to set free the ionic sodium.

I find that in annelids, barnacles (*Lepas*), ctenophores, and medusæ, the sodium of the sea-water is a strong neuro-muscular stimulant while the magnesium, calcium and potassium are inhibitors and exactly counterbalance the stimulating effect of the sodium, thus permitting weak internal stimuli to produce movements.

It is, however, remarkable that the effects of the ions, sodium, magnesium, potassium, and calcium, upon the movements of cilia of infusoria, vertebrate spermatozoa, marine larvæ and ctenophores is always the *exact opposite* of their effect upon the neuro-muscular system. Thus sodium is the most powerful stimulant for the neuro-muscular, and the most potent inhibitor for ciliary movement. Similarly considering the ions, magnesium, potassium, and calcium, among themselves, magnesium is most powerful in maintaining ciliary movement, but is the greatest depressant for the neuro-muscular system. Potassium in weak concentration at first stimulates but soon depresses neuro-muscular movements, while conversely it first depresses and then permits ciliary movement. In slightly stronger concentration it at once depresses neuro-muscular, and stimulates ciliary movement. Calcium depresses muscular, but permits of ciliary movement.

Thus in neuro-muscular movements the *stimulus* of sodium is offset by the depression of magnesium, potassium and calcium while in ciliary movement the *depressant effect* of sodium is offset by the stimulating influence of magnesium, potassium and calcium

While there is wide diversity in the reactions of motile fungi and algæ to these ions, I have found a *Spirillum* living in fresh-water which reacts as do the cilia of animals.

It thus seems possible that the ciliary movements of animals may have been taken over from motile plant-like ancestors and maintained unchanged, whereas their neuro-muscular movements have been developed later, and are controlled by the ions of the blood salts in a manner the exact reverse of cilia.

SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF THE COMMUNICATIONS.

Thirty sixth meeting.

The Rockefeller Institute for Medical Research. December 15, 1909. President Lee in the chair.

14 (424)

The value of the conglutination reaction as a means of diagnosis of acute bacterial infections.

By **FREDERICK P. GAY** and **WILLIAM P. LUCAS.**

[*From the Harvard Medical School.*]

In connection with the work on the relation of sensitizers to the alexin in 1906, Bordet and Gay described the presence in bovine serum of a substance to which the name of "colloid" was given. This colloidal substance had the property of producing a characteristic clumping of red blood cells and of accelerating their lysis when they had been treated with both a sensitizer and an alexin; its action was possible under no other circumstance. To this substance the name of "conglutinin" was subsequently given by Bordet and Streng, perhaps somewhat inadvisedly as the term had been used to describe the agglutination of blood cells by ricin. At about the same time a probably similar substance was described in goat serum by Manwaring to which the name of "auxilysin" was given, but the description of its mode of action has remained insufficient for identifying it with the colloidal substance of Bordet and Gay. In 1908 Streng was able to reproduce the phenomenon of conglutination in bacteria that had been treated with a specific sensitizer and an alexin, on the addition of bovine serum from which the normal agglutinins had been removed, if such were present. He further suggests the possible use of this reaction in the diagnosis of infections such as typhoid fever, in which case the blood of the patient would serve as the sensitizing serum.

During the past summer the matter was thoroughly considered by one of us (Lucas) in collaboration with Drs. Schorer and Fitz-Gerald in a comparative study which was made of methods of serum diagnosis in acute bacillary dysentery in infants. In this series of cases, shortly to be reported in full, a bacteriological examination was made of the stools for the presence of one or more types of Bacillus dysenteriæ and a comparative study of the reactions of agglutination, fixation, and conglutination made with the serum of each case, and usually at intervals in the course of a given case. From 45 cases of infantile dysentery, dysentery bacilli were isolated in 84.4 per cent. and in 35 of these bacteriologically positive cases, mannit fermenting organisms alone were present. In every case the three reactions with the serum were tested both with a mannit fermenting (Flexner) and a mannit non-fermenting (Shiga) strain of the dysentery bacillus. Positive reactions with the Flexner strain were much more frequent than with the Shiga strain; this may be due not only to a direct relation of the organisms concerned in producing the infection, but also, in all probability, to a greater susceptibility of the Flexner organism to the action of serum. Fifteen control cases which gave no evidence of having suffered from dysentery were also studied both bacteriologically and from the standpoint of serum diagnosis.

A positive reaction of agglutination was obtained with the serum of one control case to the Flexner organism, but in none of them to the Shiga organism. A positive agglutination reaction with the Flexner strain was obtained in 55.5 per cent. of the positive cases ranging from 9 per cent. during the first four days of the disease, to 75 per cent. in the third week. In about half as many cases a reaction was obtained with the Shiga organism. Fixation reactions were obtained with the Flexner, but not with the Shiga strain in over a quarter of the control cases (28.5 per cent.). The reaction occurred with both Flexner and Shiga organisms about equally in from 50 to 60 per cent. of the positive cases subsequent to the first week. No positive conglutination reaction was obtained in control cases, although in a few instances a reaction in a dilution of 1–40 did occur which was arbitrarily chosen as the limit of a doubtful reaction, beyond which a reaction was called "positive." The conglutination reaction appeared in 63.1 per cent. of the

positive cases with the Flexner organism. In addition, conglutination was obtained with this organism in *50 per cent. of the cases during the first four days of the disease.* Reactions of conglutination with the Shiga type were absolutely and relatively fewer than by the other methods, which would seem to indicate a more absolute specificity for this reaction. The reaction, when present, occurs usually in very high dilutions (up to 1–800) and is not to be confused with agglutination, as it frequently occurs when agglutination is absent in dilutions of 1–20, and may fail to occur when agglutinations are positive. Inasmuch as bovine serum contains a normal agglutinin for the dysentery bacillus, it is necessary to work with a preperation from bovine serum obtained by saturating with dysentery bacilli or by separating out by dialysis the insoluble proteids which contain the conglutinin but not the agglutinin (Streng).

As complementary to this work on infantile dysentery, a number of convalescent cases of dysentery from the Danvers State Hospital have recently been examined by Dr. M. M. Canavan under our direction. Dr. Canavan found that in these cases which had suffered from dysentery from one and a half years to one month previously, the agglutination reaction was present with the Flexner strain in 10 of 14 cases and with the Shiga organism in 3 cases. The conglutination reaction was present with the Flexner organism in the same number of cases (10) although not in the same cases in which the agglutination was positive. Conglutination reaction with the Shiga organism was present in one case only. It is interesting to note that in one case which had had an attack of dysentery one and a half years previously, the conglutination reaction was present with the Flexner organism, although agglutination was negative. Agglutination reactions had been obtained a month previously in this case with both organisms in low dilutions. In 8 control cases from the same institution no conglutination reaction was obtained with either organism.

We have recently considered this reaction as a means of diagnosis in typhoid fever. We have met with a number of technical difficulties and for this reason are not able to recommend the reaction as yet as thoroughly serviceable. Our findings, however,

have been constantly indicative of its ultimate value. In every set of experiments we have controlled our tests by determining the limit of agglutination with the typhoid serum and by testing for conglutination with alexin plus conglutinin alone, and also with various dilutions of a normal serum. In certain of our experiments we have obtained positive reactions without the presence of a typhoid serum, owing either to a great susceptibility of the organism used as a reagent, or else to the presence of a normal sensitizer as well as an alexin in the fresh serum of the guinea-pig employed. In many of our experiments, however, we have met with clear cut positive reactions with typhoid sera alone which, in point of dilution, ran far higher than the control agglutination reactions and which failed to occur in the controls without serum or with dilutions of normal serum. It seems at the present moment unwise to use a formolinized culture of the typhoid bacillus as we did with dysentery, as it tends to sediment spontaneously. It may be mentioned that in one case of typhoid fever a conglutination reaction was obtained on the second and third days, whereas a blood culture was negative on the fifth day and the Widal reaction did not appear until the ninth day.

A few preliminary results with cases of acute tuberculosis offer hope that the reaction may also be of value in the diagnosis of at least certain forms of this disease. Our results on this subject, however, are not sufficient to warrant a communication.

It would seem to be indicated, then, that the reaction of conglutination may prove of superior value to the agglutination reaction in the diagnosis of acute bacterial infections, both on account of its greater constancy and its early occurrence in the disease.

15 (425)

Analysis of the cleavage products of the nucleoprotein of the mammary glands.

By **J. A. MANDEL.**

[*From the Chemical Laboratory of the New York University and Bellevue Hospital Medical College.*]

Many theories as to the origin of casein in milk have been discussed in the past and for the present we have no positive ex-

perimental evidence of the origin of this important constituent of the milk. The theory of Basch that casein is formed by an action of the nucleic acid of the mammary gland upon the protein of the blood plasma has been shown to be untenable by the researches of Mandel and Levene and by Loebisch upon the nucleic acid of the mammary glands.

In order to determine, if possible, the relationship of the cell substance of the glands to the casein, I prepared the nucleoprotein of the glands according to Hammarsten's method and purified the product by solution in sodium carbonate and reprecipitation with acetic acid several times. The product obtained on purification differed materially as shown below from the same product reported by Odenius and prepared by the same method.

	Odenius.	Mandel.
Nitrogen	17.280 per cent.	15.720 per cent.
Phosphorus	0.277 "	0.551 "
Sulphur	0.890 "	trace

In order to compare the constitution of this nucleoprotein with casein, the amino acids in several portions were determined by the ordinary methods, after hydrolysis with hydrochloric acid and sulphuric acid and the average results given below obtained. The purine bases and the pyrimidine bases were also determined as given.

	Nucleoprotein.	Casein.
Glycocoll	0.00 per cent.	0.00 per cent.
Leucine } Valine }	8.15 "	10.50 "
Glutamic acid	8.58 "	11.00 "
Tyrosine	2.47 "	4.55 "
Tryptophan	present	1.50 "
Lysine	4.111 "	5.80 "
Arginine	3.021 "	4.84 "
Histidine	3.064 "	2.59 "
Guanine	1.725 "	
Adenine	0.930 "	
Thymine	0.346 "	
Cytosine	0.732 "	

On comparison with the figures given by Abderhalden and Fischer for the monamino acids and by Hart for the hexon bases we see that there is a striking correspondence in constitution between the casein and the nucleoprotein of the cell substance.

This correspondence seems to be a strong proof that the casein of the milk is formed by a breaking down of the nucleoprotein of the cell protoplasm with a setting free of the carbohydrate and the purine and pyrimidine bases.

16 (426)

Respiration by continuous intra-tracheal insufflation of air. A demonstration.

By **S. J. MELTZER** and **J. AUER**.

At the April meeting of this year, we reported that by means of continuous intra-tracheal insufflation of air, we succeeded in keeping up the life of curarized animals. We do not intend to discuss now this subject theoretically, but wish to demonstrate this method in its simplified form.

A stomach tube, having only one opening at its lower end, is introduced, through mouth and larynx, in the upper end of the right bronchus. The outside end of the tube is connected by means of a T-tube with a manometer and a bottle containing ether. This bottle is connected with glass blowers bellows, which are so handled that the pressure is kept up at about 15 millimeters of mercury. The dog has been operated nearly two hours before and the thorax has been opened transversely, so that lung and heart are freely exposed. The lungs are continuously moderately distended and quiet and the heart beats strongly and regularly.

The principle of this method differs from that of Brauer (and others) that the greatest part of the "dead space" of the respiratory path is eliminated, that the pressure is not static but dynamic, the air being continuously driven in by this pressure, and that the carbon dioxide is continuously driven out from the trachea by the same pressure, instead, as in the Brauer method, of escaping against a higher pressure.

A good many dogs were operated by this method; none had bronchitis or pneumonia. Under aseptic precautions, many survived various profound surgical procedures (in the hands of Dr. Carrel and Dr. Elsberg). We may add that no animal died from ether, even when used very freely, and that no vomiting occurred.

17 (427)

Demonstration of animals whose thoracic organs have been operated upon.

By **ALEXIS CARREL.**

[*From the Laboratories of the Rockefeller Institute for Medical Research, New York.*]

The animals have been operated upon by the method of Meltzer. At first, a few relatively simple experiments were performed, such as the resection of a pulmonary lobe, the extirpation of a segment of the middle part of the esophagus, the dissection of the mediastinum by opening the two pleuræ and the pericardium, and resection of a small part of the superior vena cava and its replacement by a piece of a jugular vein. The animals recovered completely with the exception of one which died of pleurisy a few days after the operation.

Then I began some researches on the surgery of the thoracic aorta. Six animals were operated on. In three experiments, the upper part of the descending aorta was cut transversely and sutured. The three animals recovered without incident.

In the fourth experiment, the ascending part of the aorta was cut longitudinally about three centimeters above the heart and sutured. The animal is now in good health.

The fifth experiment consisted in severing the ascending aorta in its middle part and in interposing between its ends a segment of a large jugular vein, preserved in cold storage. The circulation was interrupted for seventeen minutes. The animal remained in excellent health, but the hind legs became contractured, the animal walking as if it had wooden legs. The contracture decreased progressively. Nevertheless, at the present time, six weeks after the operation, the legs are yet a little stiff.

Then I performed a sixth experiment with temporary tubing of the aorta in order to avoid medullary complications. The upper part of the descending aorta was laid open by a longitudinal incision, and a paraffined tube was inserted into its lumen and temporarily fastened. This small operation involved only a short interruption of the circulation. The circulation was imme-

diately reëstablished, and it was possible to extirpate leisurely the anterior wall of the part of the aorta that had been tubed and to substitute for it a segment of vena cava preserved in cold storage. This operation lasted twenty-four minutes. The tube was then taken out. The animal recovered without incident. He died suddenly of hemorrhage twelve days after the operation. The accident was due to a fault of technique in preserving the veins in cold storage.

These experiments show that operations on the thoracic aorta need not be very dangerous, and that, by Meltzer's method, they are as simple as abdominal operations.

18 (428)

The mutual antagonistic life-saving action of barium and magnesium. A demonstration.

By **DON R. JOSEPH** and **S. J. MELTZER.**

[*From the Department of Physiology and Pharmacology of the Laboratories of the Rockefeller Institute for Medical Research.*]

For rabbits, 1.2 grams of magnesium sulphate per kilo body-weight are invariably fatal in intramuscular injection; they usually die in less than twenty minutes. The rabbit to the right (*A*) received such a dose and has been dead for some time. The rabbit in the middle (*B*) received a similar dose of magnesium and is still alive; it breathes regularly. This animal received also an intravenous injection of barium chloride, which is the cause of its surviving the fatal dose of magnesium.

By a special study we are enabled to state the mode of the antagonistic action of the barium which is this: the fatal action of magnesium is due to a paralysis of respiration and barium counteracts just this effect of magnesium. It differs from the antagonistic action of calcium inasmuch as calcium antagonizes all the effects of magnesium, while barium picks out only the respiration, the animal remaining anesthetized and paralyzed.

This surviving rabbit (*B*) illustrates, however, also another result. The rabbit to the left (*C*) is dead from a dose of barium

chloride similar to the one administered to the surviving animal (*B*). This means that the magnesium antagonizes the fatal effect of barium. We are not ready to state definitely in what way this action of magnesium is exerted. The poisonous effect of barium is due to its action upon various functions and magnesium antagonizes some of them. We are engaged in the study of the particulars of the subject.

19 (429)

A demonstration of the cause of acute anaphylactic death in guinea pigs.

By **J. Auer** and **P. A. Lewis.**

[*From the Department of Physiology and Pharmacology of the Laboratories of the Rockefeller Institute for Medical Research.*]

In a preliminary communication,[1] we pointed out among other things, (1) that the acute anaphylactic death of guinea pigs was due to asphyxia; (2) that this asphyxia was caused by the development of a stenosis in the pulmonary air passages, so that practically no air enters or leaves the lung in spite of violent diaphragmatic contractions, the lungs remaining distended even after opening of the chest; (3) that this stenosis was caused by a *peripheral* action of the second or toxic injection, for the same stenosis and striking lung picture was obtained after destruction of the cord and medulla, artificial respiration being maintained; (4) that this stenosis was probably caused by a tetanic contraction of the muscles of the bronchioli.

In the demonstration, a sensitized guinea pig was immobilized by curarin and artificial respiration instituted. This respiration was of such a strength that the chest expanded and collapsed well. Within from one to two minutes after the injection of one cubic centimeter of normal horse serum, the respiratory oscillations of the chest gradually became less and less and finally stopped, although the respiration machine delivered the air with the same rate, strength and amount as before; now the chest remained motionless in an inspiratory condition, thus demonstrating that the

[1] Auer and Lewis, *Jour. of the American Med. Assoc.*, 1909, liii, 458.

entering air found an obstruction or stenosis shortly after the injection of the toxic dose.

Autopsy showed the typical picture of the lungs: trachea is clear, lungs are well distended, almost forming a cast of the thoracic cavity; there is failure to collapse upon opening the chest and excising the lungs; pieces cut off from the lung do not collapse, but show on pressure a good amount of air and practically no fluid; blood in lungs and heart is black.

20 (430)
Anaphylactic "shock" in the dog.[1]

By **RICHARD M. PEARCE** and **A. B. EISENBREY.**

[*From the Carnegie Laboratory of the New York University and Bellevue Hospital Medical College.*]

The observation concerning the blood pressure here offered is not original in that the condition of low blood pressure in anaphylactic shock has previously been described by Biedl and Kraus.[2] The phenomena of anaphylactic "shock" in the dog are, however, so different from anaphylactic death in the guinea pig that it seemed to Drs. Auer and Lewis[3] and ourselves desirable, that our work, though as yet incomplete, should be presented at this time. In the dog the chief disturbance which can be demonstrated by physiological methods is a sharp fall in blood pressure (50 to 70 mm. Hg) which continues for hours, resembling in this respect shock due to other conditions. This is unaccompanied by disturbance in heart rate or by respiratory disturbance, other than that due to the medullary anemia consequent upon the low arterial pressure. From this condition the dog eventually recovers. Death has not been observed in our experiments and Biedl and Kraus state that the animals recover. The recovery from the low level of pressure is very slow, frequently no change being observed in half an hour; at other times the upward trend begins in less time.

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[1] Aided by a grant from the Rockefeller Institute for Medical Research.

[2] Biedl, A., and Kraus, R., Experimentelle Studien über Anaphylaxie, *Wiener klin. Woch.*, 1909, xxii, 363.

[3] Auer, J., and Lewis, P. A., Acute Anaphylactic Death in Guinea Pigs. Its Cause and Possible Prevention; a Preliminary Note. *Jour. of the American Med. Assn.*, 1909, liii, 458.

The increased rapidity of respiration, sometimes spasmodic in character, is transient and occurs after the fall in blood pressure begins. It is thus secondary to the change in blood pressure and possibly to be explained by the effect of the latter on the respiratory center. After the adjustment to low pressure is reached, the respirations are of normal rhythm though shallow. No changes in the lungs, which collapse upon opening the thorax, have been found.

Oncometric studies of the kidney, spleen and intestine have shown that the volume of these organs is diminished. This decrease in volume corresponds sharply in time and extent to the fall of blood pressure. A cannula in the iliac vein shows a slight increase in venous pressure (6 to 10 mm. of water). It is evident therefore that the accumulation of blood occurs in the large venous trunks of the abdomen and in the liver which at autopsy shows intense congestion.

Although our study is not complete, we consider the essential feature of this vascular disturbance, as did Biedl and Kraus, to be a loss of tone of the veins of the splanchnic area. It is of great interest that Drs. Auer and Lewis explain the respiratory disturbance in the guinea pig as due to a constriction of the smooth muscle of the bronchioles while, in the ultimate analysis, the disturbance in the dog is characterized by a paralysis of the smooth muscle of the blood vessels. Although in the two animals, different sets of smooth muscle are affected and affected in different ways, it is significant that the phenomena of anaphylaxis which are most readily studied by physiological methods are both characterized by a disturbance of the functions of smooth muscle.

Incidentally we have confirmed the observations of Biedl and Kraus that anaphylactic shock closely resembles the blood pressure changes following the injection of Witte's peptone and also that, in the dog, the blood after the administration of the toxic dose has lost its power of coagulation.

All experiments were made upon animals sensitized to normal horse serum injected in dose of five cubic centimeters subcutaneously The toxic dose was given intravenously after about twenty-one days in amounts ranging from two to six cubic centimeters.

21 (431)

The cause of serum anaphylactic shock and some methods of alleviating it.

By **JOHN F. ANDERSON** and **W. H. SCHULTZ.**

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Last July a series of experiments was begun to find out, if possible, the main cause of anaphylactic shock. It was already known that the phenomena were primarily respiratory, but it was not proven whether the origin of the trouble was central or peripheral. In order to clear up this point a number of guinea pigs were given artificial respiration, and their blood-pressure recorded from the carotid by means of a mercury manometer. It was proven that the cause of death is asphyxia which is peripheral in origin. Some animals died in spite of all that could be done for them while in others the symptoms were less acute and yielded to certain forms of treatment. In the more acute forms of anaphylactic shock the respiratory muscles of the chest and the diaphragm act without the lungs fulfilling their function. That the latter do not function is shown both by the slight motion of the respiratory tambour, connected with the trachea, and by the dark venous color of the carotid blood. In spite of the dyspneic movements the animal gradually dies from weak heart resulting probably from the lack of oxygen supply. In the less acute forms of shock, however, we were able to save the animals by artificial respiration, recovery being indicated by the carotid blood assuming its normal color, the blood-pressure returning to normal and instead of the spasmodic action of the diaphragm there ensued an even, rhythmic respiration. It was also noted that in those cases not yielding to artificial respiration the chest became fixed and the rhythmic action of the bellows caused no change in the position of the walls of the chest cavity.

About this time Auer and Lewis [1] published a preliminary note in the August number of the *Journal of the American Medical Association* stating that this asphyxia is due to an inspiratory immobilization of the lungs, since, as they suggest, the lungs, upon

[1] Acute Anaphylactic Death in Guinea Pigs. Its Cause and Possible Prevention; a Preliminary Note. *Jour. of the American Med. Assn.*, 1909, liii, 458.

being exposed, scarcely collapsed; they almost, indeed, fill the chest cavity. They found that the lungs are pink and float lightly on water; pieces cut off remain distended, the cut surfaces being moderately dry when pressed give up considerable air. This immobility of the lungs in a more or less inspiratory condition they think is due probably to a tetanic contraction of the musculature of the fine bronchioli and alveolar ducts, imprisoning the air in the alveolar sacs, and that a slight degree of pulmonary edema aids in the production of this pulmonary inspiratory immobility. They also show that subcutaneous doses of 0.5 to 1 mg. of atropin sulphate administered a few minutes previous to the killing dose of horse serum abolishes the pulmonary symptoms or greatly reduces them.

Thus far our work confirms their description of the pulmonary symptoms. We find that the lungs of pigs that die in from two to five minutes after injecting intravenously 0.5 c.c. of horse serum, are almost invariably pink, full of air, and the pulmonary blood vessels filled with blood so that if immediately after death the lungs be punctured with a lead pencil or probe, a copious flow of black venous blood results. The lungs if cut from the chest cavity remain distended and when squeezed much air and some liquid exude. Out of all the controls that died in from two to five minutes there was no exception to this rule. When pigs die after a longer time than five minutes, the lungs do not as a rule remain completely distended and do not always fill the chest cavity completely. It may almost be said (judging from the experiments thus far performed) that after the killing dose of serum the duration of life is more or less proportional to the amount of collapsible lung area left just before death. A pig then that lives more than five minutes can be made to live still longer by means that will be mentioned in the following paragraph.

The condition of *partial* lung immobilization can be initiated by certain drugs that are known to act upon smooth muscle. Atropin in small doses (.01 mg. per gm. of body weight) proves very serviceable in hindering the anaphylactic action of the serum. Thus far we have found chloral hydrate and adrenalin even more effective in desensitizing the lungs towards the second injection of serum. And when oxygen is given before the second serum injection, the lungs thereby being, previous to the injection, loaded

with a supply of oxygen, the animal is often able to pass over the first critical stage of anaphylactic shock, and if sufficient lung area is left, the heart not weakened, and the vaso-motor apparatus left intact so as not to incur too low a blood pressure, the animal almost invariably recovers. The tables which follow will illustrate clearly the relative value of the four methods thus far found most efficient in reducing the death rate of guinea pigs, and the advantage of artificial respiration, especially when oxygen is used.

A large number of drugs have been tried, but thus far no combination seems to equal that of oxygen, adrenalin, and chloral-urethane just before injecting the serum into the jugular vein. Aside from the greater number of pigs saved by this method it is of interest to note the difference in time intervening between the moment of injecting the serum, and that of death. In almost every case artificial respiration with oxygen prolongs the life of the animal. Next in efficiency is the administration of atropin or still better oxygen and then atropin. It is well to observe that certain pigs die, in spite of the best treatment, even though one third or more collapsible lung area be left after the injection; the blood pressure of such animals if recorded will eventually be found to be very low and it gradually gets lower and lower until the animal finally dies. The cause of this seems to be primarily cardiac in origin, the heart beats being greatly diminished in rate and force. There is also some evidence of vaso-dilation and of venous congestion. These are in brief the points which our present experiments indicate and it is left for a subsequent paper to treat more in detail the effects of various factors influencing anaphylactic shock.

In conclusion it may be said that in the light of the experiments thus far performed the cause of sudden death from serum anaphylaxis is due to asphyxia. The asphyxia is peripheral in origin, and in all probability Auer and Lewis are correct in attributing the asphyxia to tetanic contraction of the muscles of the bronchiolæ and alveolar ducts, thereby not admitting of further ventilation of the alveolæ. This condition of inspiratory immobilization may be greatly allayed and even abolished by certain drugs. Thus far with very sensitive pigs it has been possible to save with atropin sulphate about 28 per cent., with injections of chloralhydrate plus urethane and adrenalin, 41 per cent., by ad-

ministering pure oxygen, 43 per cent., and by administering pure oxygen along with chloralhydrate and adrenalin, even 66 per cent. Almost invariably the life may be prolonged, the pigs eventually dying from low blood pressure and not from acute asphyxia.

The pigs used in these experiments were sensitized by injecting intraorbitally 0.01 c.c. of horse serum. Young pigs, weighing about 300 grams, were injected with 0.5 c.c. of the same horse serum after having been sensitized about 30 days. Pigs were never used sooner than 21 days from the time of injecting the first dose of serum. All injections, except the sensitizing one of serum, of epinephrin and of atropin were made into a special canula tied in the jugular vein. The epinephrin and atropin were usually injected intraperitoneally.

TABLE I.

Atropin Sulphate 0.01 Milligram per Gram of Body Weight.

No.	Lived.[1]	No.	Controls Lived.
61	4 minutes.		
64	5 "		
66	5 "		
68	5 "		
70	4 "		
132	23 "	136	5 minutes.
135	+	150	4 "
139	140 minutes.	151	3 "
143	+	152	15–16 hours.
145	16 minutes.	153	3 minutes.
155	4 "	156	5 "
158	+	159	+
161	+	162	+
164	4 minutes.	165	4 minutes.

4 out of 14 lived.

TABLE II.

Chloralhydrate + Urethane and Epinephrin.

No.	Lived.[1]	No.	Controls Lived.[1]
107	+	115	5 minutes.
108	5 minutes.	116	4 "
109	+	117	5 "
110	5 minutes.	118	5 "
111	6 "	119	5 "
112	+	120	+
113	+	121	5 minutes.
114	5 minutes.	122	4 "
125	5 "	123	3 "
127	6 "	124	5 "
128	+	126	+
130	9 minutes.	129	6 minutes.

5 out of 12 lived. 2 out of 12 lived.

[1] The sign + in these tables indicates complete recovery, the animal being kept for observation a week or longer. The number of minutes given in the second column is the interval of time between the moment of injecting the killing dose of serum and the final gasp.

TABLE III.

Artificial Respiration with Oxygen Alone.

No.	Lived.	No.	Controls Lived.
72	+	78	+
73	+	79	3 minutes.
74	+	80	2 "
75	+	81	4 "
76	60 minutes.	82	4 "
77	+	83	3 "
84	+	89	4 "
86	35 minutes.	93	5 "
87	28 "	94	4 "
88	8 "	95	3 "
90	+	96	9 "
91	105 minutes.	97	5 "
92	31 "	99	3 "
98	64 "	101	+
100	93 "	103	+
102	16 "	104	2 minutes.
	7 out of 16 lived.		3 out of 16 lived.

TABLE IV.

Artificial Respiration with Oxygen Accompanied by Injections of Epinephrin and Chloralhydrate-Urethane Solutions.

No.	Lived.	No.	Controls Lived.
138	+	146	5 minutes.
141	+	147	4 "
142	+	148	5 "
144	+	149	3 "
154	+	152	+
157	+	156	5 minutes.
160	37 minutes.	167	+
163	+	168	4 minutes.
170	14 minutes.	169	4 "
172	+	171	5 "
174	51 minutes.	173	4 "
176	98 "	175	6 "
		177	4 "
	8 out of 12 lived.		2 out of 13 lived.

22 (432)

The influence of glycerin on gastric secretion.

By **L. KAST.**

[*From the Medical Department, New York Post-Graduate Medical School.*]

If the gastric mucosa of the living dog is exposed for a short time to from one to two per cent. of glycerin in water, the gastric secretion which follows is not more intense than after water

alone. Three years ago I observed this experimentally in the Laboratory of the Pathological Institute of Berlin, and last year it was confirmed by Rodari. In experiments with stronger concentrations of glycerin, especially if allowed to enter the duodenum, the gastric secretion which follows is less than after pure water. Glycerin furthermore not only reduces the gastric secretion incited by water, but inhibits even a subsequent secretion of the stomach provoked by sham-feeding. This I have observed in an experiment on a dog with sham-feeding; the influence of glycerin on the human stomach does not appear to have been the subject of study.

Up to the present I have examined the influence of glycerin on gastric secretion in twenty-one patients, some of whom suffered from gastric disturbances, some from other affections, and from this material I have collected the results of seventy-two experiments. The patient received a simple test breakfast, and subsequently, under otherwise identical conditions, a similar test breakfast with the addition of from 30 to 45 cubic centimeters of glycerin. The two test meals were administered either on the same day or on different days, and when the former method was employed, at least four examinations were made; one day the simple test meal was given first and the other day the glycerin test meal was given first. Of these twenty-one patients sixteen showed a diminished total acidity after glycerin of from 3 to 50 per cent. of their acidity; in four patients the results were irregular; and in one patient there was only an increased secretion of hydrochloric acid after the ingestion of glycerin.

It may, therefore, be assumed that glycerin reduces gastric secretion in the majority of cases, and this was especially noticeable in cases with subjective or objective signs of hyperacidity.

Pawlow has demonstrated that neutral fat reduces both the motility and the secretion of the stomach. Possibly neutral fat, as such, does inhibit the secretion, but it is also possible that a cleavage product of the fat may have the same effect. If such is the case — and it has been shown that the stomach splits fat into fatty acids and glycerin to some extent — then the glycerin component is the inhibiting factor, because, according to Pawlow, soaps and fatty acids excite the gastric secretion from the duodenum. Should my experiments be confirmed glycerin would have to be

considered a substance of our food which reduces gastric secretion from the stomach, and more so from the duodenum and the small intestine. Possibly the depressing effect of fat upon gastric secretion, as discovered by Pawlow, resolves itself into the mere effect of its division product, glycerin.

Aside from glycerin, there are two other kinds of alcohol, namely, amyl and butyl alcohol, that I have observed to have an inhibitory effect upon gastric secretion.

23 (433)

The summation of stimuli.

By **FREDERIC S. LEE** and **MAX MORSE**.

[*From the Department of Physiology of Columbia University at the College of Physicians and Surgeons, New York, and from the Harpswell Laboratory.*]

The phrase, "summation of stimuli," has been employed at times to signify only the phenomenon in which a stimulus of a fixed intensity, which at first is too weak to stimulate living substance, will upon repetition be followed by a response. It is more rational to include within the concept all cases of summation, whether the stimulus is at first below the stimulation threshold or above it. Summation is usually ascribed to an increase in the irritability of the protoplasm, but the conditions responsible for such increase have not been known. Two years ago, the senior author explained the increase in irritability found in the treppe of muscle, by the augmenting action of fatigue substances, notably carbon dioxide and lactic acid. This chemical theory of the treppe is here applied to the explanation of summation in general. The validity of this explanation has been confirmed by a large variety of experiments performed on the muscles of medusæ and crustaceans. It has long been known that summation with subminimal stimuli is very readily obtained in these forms. The authors have confirmed this. They have also studied the action on the muscles of carbon dioxide and lactic acid in small quantities. When a stimulus was found that was just too weak to cause contraction, carbon dioxide was administered to the muscle for a period of a few seconds, either in solution or as a gas. The hitherto subminimal stimulus was then

found to be supraminimal and at times even maximal. A similar result was obtained with lactic acid, which was administered to the muscle in an isotonic solution of various salts. When lactic acid in a strength of 1/3200, or even 1/6400, gram-molecular solution, was injected into the muscle, a stimulus heretofore subminimal immediately elicited contractions. Thus both carbon dioxide and lactic acid in small quantity are capable of increasing the irritability of protoplasm. Gotschlich found that continued subminimal stimulation of muscle renders it acid in reaction, even though no contractions occurred. The conclusion therefore seems to be justified that summation of stimuli may be explained as due to a rise in irritability, brought about by the action on the living substance of small quantities of certain products of metabolism, especially carbon dioxide and lactic acid, the same substances which, in larger quantity, are important factors in fatigue.

24 (434)

The action of magnesium salts: A. In relation to motor nerve impulses; B. In relation to sensory stimulation.

By **A. H. RYAN, F. V. GUTHRIE** and **C. C. GUTHRIE.**

[*From the Physiological Laboratories of Washington and Pittsburgh Universities.*]

Since 1869 it has been generally held that magnesium salts have a curare-like action (Jolyet and Cahours, *Arch. de physiol.*, 1869, ii, 113; Binet, *Rev. méd. de la Suisse romande*, 1892, xii, 523, 593; Wiki, *Jour. de physiol. et de path. gén.*, 1906, viii, 794–803; Bardier, *ibid.*, 1907, ix, 611, and others). As this point is of interest in connection with the behavior of animals after the subcutaneous injection of magnesium salts, we have re-investigated this phase of their action.

A. In Relation to Motor Nerve Impulses.

Frogs have for the most part been used, though some observations have been made on mammals (rabbits, dogs, cats, rats, etc.). As the results are in agreement for all animals so far tried, only those on frogs and rabbits will be mentioned here.

In the frog the femoral blood vessels in one leg were ligated and the two gastrocnemius muscles connected with levers. Stationary electrodes were placed beneath the sciatic nerves and by a suitable arrangement of keys an induced current could be led into either nerve at will. After establishing the control response in both muscles from 1.0 to 1.5 c.c. of the salt in saturated solution was introduced into the dorsal lymph sac. The nerves were stimulated at intervals and the results recorded.[1]

Results. — 1. Injection of 1.0 to 1.5 c.c. saturated solution of magnesium sulphate into the dorsal lymph sac of a 20 to 30 gram unpithed frog is soon followed by a loss of muscular response to nerve stimulation while direct stimulation of the muscle remains as effective as before the injection.

2. The limb whose blood vessels were previously ligated showed no such loss of response to nerve stimulation.

It may be remarked that it is known that other salts, *e. g.*, sodium chloride also have a curare-like action.

B. In Relation to Sensory Stimulation.

After ligating the femoral blood vessels to one leg in frogs, the response to sensory stimulation, *e. g.*, thermal, electrical, chemical (acid) and mechanical stimulation of the skin of the fore and hind limbs was recorded by contraction of the gastrocnemius muscles. Magnesium salts, 1.0 to 1.5 c.c. saturated solution, were then injected into the dorsal lymph sac. After a time no response in the unligated leg could be elicited by stimulating as before, but the muscles in the ligated limb responded strongly. At this stage the muscles in the unligated leg responded strongly to direct stimulation, but not at all to nerve stimulation. In such an experiment at this stage the animal is still breathing well and there are no indications of insensibility.

A rabbit was poisoned with magnesium salt solution administered subcutaneously. After a time one sciatic nerve was exposed and stimulated with an induced current. Upon stimulation of the sciatic nerve, reflex contraction of the muscles of the trunk occurred while only slight or no response of the muscles supplied by this nerve was observed. Direct stimulation of the muscles

[1] Detailed descriptions of the apparatus and technique employed will be included with the complete account of these experiments.

with a current of the same strength brought a good response. At this time the animal was breathing well and there were none of the symptoms of asphyxia which appeared later.

Results. — 1. The behavior of an animal in response to sensory stimulation is notably altered after the subcutaneous injection of magnesium salts in large amounts. Motor response may even entirely disappear but a disappearance of sensitiveness is not concomitant with motor paralysis. But if previous to the administration of the salt in frog, the blood vessels to a hind limb be ligated, the muscles of such a limb show good response to stimulation of the skin of the fore limbs.

2. A rabbit poisoned with magnesium sulphate shows a loss of muscular response to indirect stimulation, while at this time the muscular response to direct stimulation is good. At this stage the reflex mechanism is still capable of functioning as shown by the contraction of trunk muscles on stimulating the central end of the sciatic nerve. The more peripheral muscles seem first to be paralyzed. The muscles of respiration appear to be the last to become paralyzed.

25 (435)

The effects of direct application of magnesium salts: A. To motor and sensory nerves; B. To cardio-inhibitory nerves.

By **C. C. GUTHRIE, F. V. GUTHRIE** and **A. H. RYAN**.

[*From the Physiological Laboratories of Washington and Pittsburgh Universities.*]

A. The sciatic nerves in both legs of frogs were exposed and three pairs of stationary electrodes placed beneath each. The wiring was such that an induced current could be switched to any of the six pairs of electrodes at will. After recording the control, direct and reflex response of the gastrocnemius muscles, the solution to be tested was applied to the nerve trunk at the site of one of the middle pairs of electrodes. Stimulation of the nerves was continued and the result recorded. After a time the solution on the nerve (or on both nerves, when two substances were being tested at the same time) was removed and return of function

recorded. Changes in excitability were observed by stimulating with the middle pairs of electrodes.

B. The vagus nerves of spreading vipers were isolated and stationary electrodes placed beneath each nerve. The heart (apex) was connected with a lever by means of a thread and its action recorded. After establishing the control responses to vagal stimulation by leading a current through each pair of electrodes consecutively, a saturated solution of magnesium sulphate, magnesium chloride, sodium sulphate, sodium chloride, calcium chloride or cane sugar was applied to the nerves below the electrodes and the nerves again stimulated, the nerves being washed with 0.75 per cent. sodium chloride and normal response established between each application.

Results. — 1. The direct application of strong solutions of magnesium sulphate to a mixed nerve (sciatic) is, as a rule, soon followed by contraction of the muscles supplied by the nerve; and often by contraction of the muscles of the opposite leg, as well as other muscles of the body (reflex contraction).

2. Stimulation of the nerve above and below the point to which the salt is applied gives results indicating the onset of afferent before efferent block.

3. If the salt be removed soon enough the block may disappear.

4. Other substances, *e. g.*, sodium chloride, sodium sulphate, magnesium chloride, calcium chloride, or cane sugar, give similar results.

5. In common with all the other above mentioned substances tried the application directly to the vagus nerve of a strong solution of magnesium sulphate or magnesium chloride causes a loss in conductivity in the cardiac-inhibitory fibers; and if the solution be removed soon enough conductivity may be restored.

We do not consider that any specific action of strong magnesium salts solutions on the conductivity of nerve fibers has been made out. The blocking effect does not appear to differ from that produced by any markedly hypertonic solution.

26 (436)

The survival and growth of subcutaneously engrafted ovarian and testicular tissue.

By **C. C. GUTHRIE.**

[*From the Physiological Laboratories of Washington and Pittsburgh Universities.*]

Fragments of ovaries and testicles in chickens, and testicles in guinea fowls were removed and placed beneath the skin. Other similar fragments were placed in the peritoneal cavity. After several months the engrafted tissues were examined and compared with each other and also with the tissue left in normal situation.

Results. — When engrafted in favorable situations, *i. e.*, in close proximity to large blood vessels,[1] both subcutaneous and intraperitoneal ovarian tissues make a good growth in chickens, being very similar both in gross and microscopical appearance to normal ovarian tissue. In agreement with Lode,[2] testicular tissue in chickens was found to give good results being very similar to the results for ovaries. The same was also found to be true for guinea fowls. Such engrafted tissues contained numerous spermatozoa.

Results of exchanges of such tissues between the sexes as well as between different species have thus far been negative, but it would be premature to draw definite conclusions from the results.

Using juice prepared from engrafted as well as from normal testicular tissue investigations are being made to determine the feasibility of thus artificially fertilizing hens with the view of testing for a "soma" or "foster father" influence on the sperm; and also to obtain more data on the rôle of the accessory sexual secretions.

[1] Knauer, *Cent. für Gynäkol.*, 1896, xx, 524; *Arch. für Gynäkol.*, 1900, lx, 322.
[2] Lode, *Wiener klin. Woch.*, 1895, viii, 345.

27 (437)

The survival of engrafted thyroid and renal tissue.

By **C. C. GUTHRIE.**

[*From the Physiological Laboratories of Washington and Pittsburgh Universities.*]

THYROID.

One lobe of the thyroid of a dog was removed and replaced with reversal of the circulation, *i. e.*, the central end of the superior thyroid artery was anastomosed to the peripheral end of the superior thyroid vein, and the central end of the vein was anastomosed to the peripheral end of the artery.

After a lapse of more than two years the lobes of the gland were compared and specimens were taken and examined microscopically.

Results. — The unoperated lobe in size was somewhat hypernormal (perhaps compensatory hypertrophy) and microscopically showed hyperplasia. The operated (auto-engrafted) lobe in size was hyponormal. Structurally, it was markedly fibrous; but it was found to contain cellular elements which appeared normal and normally staining colloid, the arrangements and proportions being abnormal.

KIDNEY.

In 1905 whole kidneys were engrafted in both cats and dogs with excellent temporary success, but in all cases where all the original renal tissue was removed, the animals invariably died within a few weeks. At post mortem such kidneys showed more or less degeneration. The immediate result appears to be a congestion, accompanied, in some instances at least, with more or less extensive interstitial hemorrhages. Cloudy swelling quickly ensues and later more pronounced degenerative processes leading to the disappearance of the normal cell structure.

In another experiment one kidney was removed from an adult female cat and a kidney from an adult male cat was engrafted in the place previously occupied by the kidney removed, the renal artery being anastomosed to the aorta, the renal vein to the vena cava and the ureter to the stump of the ureter previously divided.

As previously reported (*Jour. of the American Med. Assoc.*, 1908, li, 1658), the cat did not survive the functional test (removal of the remaining original kidney) made over a year later.

Results. — Structurally, the engrafted kidney was very fibrous. Histologically, a reminiscence only of normal renal structure remained, it being possible only with care to trace the glomeruli and the beginning of the tubular structures.

28 (438)

The effect of anemia and of double hyperemia on hyperplastic goitre.

By **C. C. Guthrie.**

[*From the Physiological Laboratories of Washington and Pittsburgh Universities.*]

In a dog showing a bilaterally symmetrical hyperplastic goitre, Dog 16, the following vascular changes were made:

A. Anemia, left side:
   1. Ligation of the left common carotid and superior thyroid arteries.

B. Double hyperemia, right side:
   1. Ligation of the internal jugular vein below the mouth of the inferior thyroid vein and above the superior thyroid vein (passive hyperemia).
   2. Section of the internal jugular vein below the origin of inferior thyroid vein and anastomosis of the distal end to the central end of the left common carotid artery.

Results. — Clinically, on the left side (anemic), no marked change was observed. On the right side (hyperemic), a great temporary swelling followed by a marked decrease in size of the right lobe occurred. Seven months later the left lobe measured 8 by 4.5 by 3 centimeters, and the right lobe measured 5 by 2.5 by 2 centimeters.

Structurally, the right lobe was more fibrous than the left and there appeared to be present a larger proportion of normally staining colloid.

29 (439)

A method for the determination of amino nitrogen and its applications.

By **DONALD D. VAN SLYKE.**

[*From the Rockefeller Institute for Medical Research.*]

It has long been known that aliphatic amines react with nitrous acid according to the equation $RNH_2+HNO_2=ROH+H_2O+N_2$, and several methods have been devised for estimating amino groups by measuring the nitrogen gas evolved by this reaction.[1] None of them has been sufficiently simple or accurate to attain general use, however. The method proposed requires but little apparatus, but a few minutes for completion, and is as accurate as a Dumas or Kjeldahl determination. The reaction is carried out in a bottle with a capacity of about 35 cubic centimeters, fitted with a three hole No. 4 rubber stopper. Through the stopper pass: (1) the stem of a 10 c.c. burette; (2) the thick-walled capillary inlet from a cylindrical dropping funnel of 25 c.c. capacity; the capillary is of 2 mm. internal diameter and reaches nearly to the bottom of the bottle; (3) an outlet tube for gas. This is a capillary 25 to 30 cm. high, 1 mm. internal, 5 to 6 mm. external diameter. The lower end is flush with the bottom of the stopper, the upper end is bent in a semi-circle to meet the inlet of a gas burette. The tube has a stopcock near the middle.[2]

The amino solution for analysis is placed in the burette, and a few cubic centimeters of water in the dropping funnel. Into the bottle are poured 27 c.c. of a 10 to 3 solution of sodium nitrite followed by 7 c.c. of glacial acetic acid. The stopper is placed in position and the slight air volume left in the bottle displaced by water from the dropping funnel. The outlet tube is then closed, whereupon the nitric oxide gas formed by decomposition of the nitrous acid fills the upper part of the bottle, forcing the solution back into the funnel. When from 5 to 10 c.c. of gas are thus gathered, which requires but a few seconds, the outlet is opened and the gas driven out again, washing out the remaining traces of

[1] Hans Meyer: Anleitung zur quant. Best. organischen Atomgruppen, p. 81. Fischer and Koelker, *Annalen d. Chem.*, 1905, cccxl, 177.

[2] The apparatus can be obtained from Eimer and Amend, New York.

air. This is repeated to make absolutely certain that no air remains; then the outlet is closed until a gas space of from 15 to 18 c.c. has formed. The stopcock of the dropping funnel is then closed and the outlet connected with a gas burette. The amino solution is run in from the 10 c.c. burette, and the bottle shaken at short intervals to hasten the evolution of gas. The latter is continued until 30 to 40 c.c. more gas, than the volume of nitrogen expected, is in the gas burette. The cock of the dropping funnel is then opened, and all the gas from the bottle and outlet tube displaced into the gas burette. This mixture of nitric oxide and nitrogen is now run into a Hempel pipette containing a 5 per cent. potassium permanganate 2.5 per cent. potassium hydroxide solution, which absorbs the nitrous oxide. The pure nitrogen is then measured in the burette.

Alanin, valin, leucin, glycocoll, aspartic acid, glutaminic acid, phenylalanine, serine, oxyprolin, tyrosin, arginin, histidin, tryptophan, and guanin yield one molecule each of nitrogen. Lysin yields 2 molecules of nitrogen. Prolin, being an imino substance, does not react at all. Guanidine and its derivatives also fail entirely to react.

This method will be of value for convenient analysis in identifying the amino acids, also for the estimation of the amount of amino nitrogen in unknown substances, and in mixtures such as hydrolyzed protein. It further renders possible an accurate determination of the prolin obtained by the ester method. The alcoholic extract of the amino acids, whose esters distill below 100°, contains prolin with a hitherto undeterminable amount of the other acids as impurities. The amount of these impurities can be determined by amino nitrogen estimation, and this nitrogen subtracted from the total, gives the prolin nitrogen. Histidin and arginin, as obtained in solution by the Kossel and Patten method, can be analyzed without isolation. The ratio, total N : amino N, in the case of histidin is 1 : 3, of arginin 1 : 4, and as these ratios are characteristic, amino and Kjeldahl determinations on their separate solutions are sufficient to identify these bases.

The amino nitrogen method has been made the basis of a quantitative determination of amino nitrogen (amino acids) in the urine. Urea and ammonia react slowly with nitrous acid so must

be removed; 75 c.c. of urine plus 2.5 c.c. concentrated sulphuric acid are heated in an autoclave, for one and one half hours at 175°. The urea is entirely changed to ammonia, which is boiled off after adding 10 gm. of calcium oxide and a piece of paraffin. The ammonia-free filtrate is concentrated to a small volume, diluted to 25 c.c., and amino nitrogen determinations made on 10 c.c. portions. In blank determinations, 11.55 mg. nitrogen as alanine were added to a normal urine. The increase in amino nitrogen was 11.47 and 11.58 mg. n duplicates. Determinations on a number of normal urines indicate a normal amino nitrogen of 2.0 per cent. ± 0.5 per cent. for a normal urine. The study of pathological urines is being undertaken, as the amino determination may be of value in indicating conditions where physiological oxidation of protein nitrogen is incomplete.

30 (440)

Note on the production of glycosuria by parathyroids, pancreas and the infundibular extract of the pituitary.

By ISAAC OTT, M.D., and JOHN C. SCOTT, M.D.

In experiments upon cats we have found that injection per jugular of filtered watery solution of the parathyroid or the pancreas produced 3 to 4 per cent. of sugar in the urine. Injections into abdominal cavity of the pancreas also produced glycosuria. Borchardt has shown that the pituitary gland as a whole causes sugar to appear in the urine. We have found 1 c.c. of the 20 per cent. extract of the infundibular part (Burroughs, Wellcome and Co.) of the pituitary by the jugular causes about 3 per cent. of sugar to appear in the urine. We took care that the binding down and etherization did not cause any sugar to be present in the urine of our animals. Falta and Priestly did not find any increase of the sugar in the blood of the rabbit by relatively large doses of infundibulin. The presence of glucose was always determined by Fehling's, fermentation, and phenylhydrazine tests.

31 (441)

A report on experimental poliomyelitis.

By **Simon Flexner** and **Paul A. Lewis.**

By employing as a virus the spinal cord from two human cases of epidemic poliomyelitis, it has been found possible not only to transmit the disease to monkeys, as Landsteiner and Popper[1] did, but by employing the intracerebral mode of inoculation, to propagate the disease successfully through a long series of monkeys. In this manner, epidemic poliomyelitis or infantile paralysis has been opened up to experimental study.

It has been proven conclusively that the symptoms and pathological lesions of epidemic poliomyelitis are identical with those occurring in the spontaneous disease of man. It has next been shown that the virus of poliomyelitis is effective in monkeys not only when introduced into the brain, but also when injected into a large nerve (sciatic nerve), into the circulation, into the peritoneal cavity, and beneath the skin.

In the inoculation, in any of these ways, of the virus, a definite incubation period is required before the disease develops. This period has varied in the experiments from four to thirty-three days. The symptoms which appear often arise suddenly, as they also do in the spontaneous disease of man. The experimental disease in monkeys is severe and often fatal. When recovery takes place, there usually remain residues of the paralysis, similar to the residues which have been observed in the recovery from the spontaneous disease of man.

The nature of the virus of epidemic poliomyelitis is indicated by the circumstances, first, that it withstands the action of pure glycerine for at least one week, and second, that it can be passed through a Berkefeld filter. In other words, the virus has, thus far, not been demonstrated certainly under the microscope. It is so small that it passes quite readily through a mechanical filter, and so resistant that it withstands the action of glycerine in a manner similar to the viruses of vaccinia and rabies. The present indications are, therefore, that this virus is like the viruses of the diseases mentioned and belongs to the group of optically invisible causes of disease.

[1] Landsteiner and Popper: *Zeit. f. Immunitätsforsch.*, Orig., 1909, ii, 377.

32 (442)

The depression of the ammonia destroying power of the liver after thyroid-parathyroidectomy.

By **A. J. CARLSON** and **CLARA JACOBSON.**

[*From the Hull Physiological Laboratory of the University of Chicago.*]

1. The symptoms produced by intravenous injections of ammonium carbonate and ammonium carbamate in dogs (Marfori) are practically identical with the symptoms of thyroid-parathyroidectomy in dogs, foxes and cats. The same is true of the typical symptoms of poisoning on liberal protein diet in dogs with Eck fistula or after ligation of the hepatic artery (Nencki, Pawlow, Saleski, Rothberger, Winterberg, Hawk). After parathyroidectomy in dogs there is an increase in the ammonia content of the blood (MacCallum and Voegtlin). A high protein (meat) diet with its attendant increase of ammonia in the portal blood accelerates and intensifies the tetany in thyroid-parathroidectomized dogs (Munk, Breisacher, Beebe). MacCallum and Voegtlin succeeded in obtaining tetany in only three dogs when placed on starvation. We find that in thyroid-parathyroidectomized cats the feeding of meat appears to hasten the appearance of tremors and convulsions, and that the symptoms are less severe and life is prolonged in starving animals, but this point can be settled only after very extensive experimentation because of the periodicity of the symptoms. The foregoing facts taken altogether suggest that *the tremors and convulsions usually following thyroid-parathyroidectomy in carnivora may be due to ammonia poisoning.*

2. The results of MacCallum and Voegtlin as regards the increased ammonia content in dog's blood after parathyroidectomy are confirmed on cats and foxes:

100 c.c. blood of normal cats (5 experiments) contain.....	1.54	mgr. ammonia.
100 c.c. blood thyroidectomized cats (6 experiments) contain.....	2.52	" "
100 c.c. blood normal foxes (4 experiments) contain.....	2.50	" "
100 c.c. blood thyroidectomized foxes (4 experiments) contain....	3.50	" "

In no instance was the increase as great as that recorded by MacCallum and Voegtlin for dogs. The ammonia content of normal foxes is considerably higher than that of normal cats.

3. The ammonia destroying power of the liver was determined by perfusing the excised organ for 30 minutes at 40° C. with mixture of blood (75 c.c.) and Ringer solution (225 c.c.) containing 20 mgr. ammonium carbonate per 100 c.c.

Results.	Ammonia destruction
Livers of 15 normal cats	39 per cent.
Livers of 10 thyroid-parathyroidectomized cats	13 per cent.
Depression	26 per cent.
Livers of 3 normal foxes	44 per cent.
Livers of 4 thyroid-parathyroidectomized foxes	14 per cent.
Depression	30 per cent.

The increase in ammonia in the blood after thyroid-parathyroidectomy is therefore due, at least in part, to depression of the liver rather than to acidosis. The liver depression may be due to changed conditions of the liver cells or to depressor substances in the blood. The diminished power of oxidation and decreased rate of autolysis in the liver after thyroidectomy (Stookey) point to the former alternative. These results support Beebe's hypothesis of derangement of protein metabolism.

4. In the case of the thyroid-parathyroidectomized animals (foxes) that exhibit no typical symptoms (dyspnœa, salivation, tremors, depression) there is no increase in the ammonia content of the blood and no depression of the ammonia conversion power of the liver.

5. We are not prepared to say that the percentage of ammonia increase in the blood after thyroid-parathyroidectomy is the primary factor in producing the symptoms. The increased ammonia in the blood and the loss of calcium by the central nervous system (MacCallum and Voegtlin) would probably work in the same direction as regards the production of tetany, but MacCallum's results are flatly contradicted by Cooke. On the other hand, there is probably an increase in the blood of other poisonous products of protein catabolism besides ammonia, owing to the law of mass action or to the impaired liver activity.

6. The relation of the inorganic salts of the blood and of the internal secretions of the parathyroids to the detoxication processes in the liver cells should be investigated. If the mere increase of ammonia and other protein metabolites in the blood is the cause of the apparent derangement of the magnesium (and perhaps

calcium) metabolism after thyroid-parathyroidectomy similar results ought to follow Eck fistula or ligation of the hepatic artery.

33 (443)

The relation of ptyalin concentration to the diet and to the rate of salivary secretion.

By **A. J. CARLSON** and **A. L. CRITTENDEN**.

[*From the Hull Physiological Laboratory of the University of Chicago.*]

I. *The relation of ptyalin concentration to the diet.*

a. In Man. — 1. In the fall of 1908 the diastatic power of the parotid saliva of three individuals (A. J. C., A. L. C., C. C.) designated for convenience as *A*, *B*, and *C*, was compared daily for a period of ten days. The saliva of *A* was uniformly slightly stronger than that of *B*, and considerably stronger than that of *C*. At the end of the ten-day period *B* and *C* were put on an exclusive vegetarian diet, that is, meat was excluded and the carbohydrates greatly increased, for ten days, while *A* continued on the ordinary mixed diet. The diastatic power of the parotid salivas was tested daily and *there was no increase in B and C as checked against A.*

2. The diastatic power of the parotid saliva of a man who for four years had been a consistent vegetarian was checked (for seven days) against that that of *A* and *B*. *It was uniformly less than A and practically the same as B.*

3. The parotid or mixed saliva of a boy of 14 years, a "congenital" vegetarian, never eating meat, was checked against the corresponding salivas of *A* and *B*. It showed *uniformly less diastatic power than A, and about the same as B.*

Thus, contrary to Nielson's results, there is no evidence that in man *even years of exclusion of meats and greatly increased carbohydrates in the food will appreciably increase the ptyalin concentration in the saliva.*

b. In Other Mammals. — It is conceivable that while shorter periods of meat exclusion and carbohydrate increase in the diet of man may not effect an increase in the ptyalin, generations of vegetarianism might be effective. This could be tested on the saliva of

orthodox Hindus, but we were not able to secure this material. The experiment has, however, been carried out in nature on a large scale in the case of the herbivora.

1. Carnivora. — There is no ptyalin in the saliva of the dog, the cat and the fox (6 individuals). The slight diastatic power of the saliva of these animals is due to traces of blood and lymph diastases.

2. Herbivora. — The diastatic power of the parotid and mixed saliva of monkeys (7 individuals) is the same or less than that of man. The ptyalin concentration in the rabbit's parotid saliva is the same or slightly greater than that of man. But the parotid and mixed saliva of the goat (6 individuals) and the horse (13 individuals) has no diastatic power.

3. Thus, while the absence of ptyalin in the saliva of many (probably all) carnivora and its presence in rodents and primates may suggest adaptation, the absence of it in some herbivora nullifies such a conclusion. The saliva of monkeys ought on the adaption hypothesis to have greater ptyalin concentration than that of man. But we do not wish to be understood as holding that the ptyalin producing processes have been evolved without any relation to the nature of the food, because we must have data from all the mammalian groups before we are in position to determine whether the absence of ptyalin signifies atrophy or incipient evolution.

II. *The relation of ptyalin concentration to the rate of secretion of the saliva.*

1. Weak acids (acetic) in the mouth are a more efficient stimulus to the secretion of the parotid than mechanical stimuli (dry sand, crackers, flour, cotton) and within limits the stronger the acid the greater the rate of secretion. The concentration of the human parotid saliva varies directly with the rate of secretion, just as is the case of lower mammals.

2. The concentration of the ptyalin in the parotid saliva of the rabbit varies directly with that of the organic solids in the case of gland anemia and on stimulation of the cervical sympathetic nerve (Carlson and Ryan). Since in the rested gland the organic solids increase with the rate of secretion we would expect the rapidly secreted parotid saliva to contain more ptyalin than the slowly

secreted saliva. This is the case in the individuals (man) who respond readily with varying secretion rates to stimuli of varying strength (different strength of acids, or sand and acids). Thus the slowly secreted saliva obtained on placing sand in the mouth contains less pytalin than that secured on stimulation with acid. But this direct relation between ptyalin concentration and secretion rate is not a close one, hence a great difference in secretion rate is required in order to demonstrate the difference in diastatic power. But this is also true of the organic solids. We have not yet been able to demonstrate this relation in the case of the rabbit's parotid saliva, probably because of the rapid fatigue of the gland under experimental conditions.

3. Qualitatively different stimuli (acid, salt, sweet, bitter, mechanical, agreeable, disagreeable) yield no constant difference in the ptyalin concentration of the parotid saliva in man. But these data are not conclusive owing to the practical impossibility of keeping the secretion rate uniform.

4. In varying directly with the organic solids and the secretion rate it seems that the processes of ptyalin secretion differ from the ferment-secreting processes in the other digestive glands. This may be of significance in view of the fact that ptyalin seems to be superfluous in digestion; but, again, it is not plain whether this condition signifies atrophy or incipient evolution.

Pawlow's findings that in the dog dry sand in the mouth causes a rapid secretion of a very dilute saliva seem not to apply to man. In man the secretion rate varies directly with the strength of the stimulus in the mouth and the saliva concentration depends — within limits — on the secretion rate. There may be some difference in different mammalian groups as regards the efficacy of the different reflex stimuli in the mouth, as acids in the mouth do not produce a copious salivary flow from the rabbit's parotid.

Unless the factor of secretion rate is controlled in all work on saliva concentration and ptyalin concentration under different reflex stimuli and dietary conditions, the results obtained are not conclusive.

34 (444)

On non-specific complement fixation.

By **Hideyo Noguchi.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

Complement is fixable by various substances. It is fixed by different extracts containing certain proteins. Fixation in this case is direct and *non-specific*. On the other hand, complement is also fixed by a combination of *specific* antigens and antibodies (Bordet-Gengou). In the last instance, fixation is accomplished by the coöperation of the antigen and antibodies, the latter being inert without the aid of each other. From this observation the deduction was formed that whenever complement is fixed by a mixture of two substances, it is an expression of a specific reaction taking place in such a mixture. This assumption, however, is permissible only when the above phenomenon can be produced by none but the specific antigens and antibodies.

Recently I encountered a peculiar phenomenon which resembles very closely the true Bordet-Gengou reactions, differing from the latter in the non-specific nature of the substances serving as antigen. Working on the sera of tuberculous patients, using tuberculin and the nucleoprotein of tubercle bacilli as antigen, I found that twenty out of twenty-five cases gave complement fixation in varying degrees when tested in unheated state. Encouraged by this result, I examined thirty-five control cases without tuberculosis and found, to my surprise, that twenty-eight of these gave positive reactions with the same antigen.

A subsequent study revealed that pepton, albumoses, glycogen, various extracts of bacteria, tissues and organs, and certain cleavage products of protein[1] gave similar fixation phenomena. Thus the phenomenon is found to be non-specific and is due to the addition of these substances to active human sera and it is present in a majority of human sera.

[1] I am greatly indebted to Dr. P. A. Levene who placed these substances at my disposal. Among these may be mentioned allanin, glycil-glycin, leucin, tyrosin, glycocoll; these have, however, less fixing power than higher protein molecules and glycogen.

This non-specific fixation of complement can be avoided by inactivating the sera before testing. *From the above finding it follows that no complement fixation test, with a view of obtaining a specific reaction, should be made with unheated serum. On the other hand, the Wassermann reaction can be carried out with active human sera when the antigen does not contain those substances which are found to give a non-specific reaction with the active sera.*

I usually use in my system of the Wassermann reaction active sera and pure lipoids free from proteins and have never obtained the so-called *non-specific reaction.* It is not possible, however, to obtain reliable results if one uses aqueous or alcoholic extracts of liver as antigen, because these extracts contain the disturbing proteins already referred to. When one intends to use aqueous or alcoholic extracts as antigen, the patient's serum should be inactivated before using. In a recent article by Swift, I noticed that he obtained positive reactions in certain non-syphilitic cases by employing my method and he states that this can be avoided by using inactivated sera. I would like to call attention to the fact that he used alcoholic extracts and not pure lipoids (acetone-insoluble fractions as recommended by me) in the former of which there exist large quantities of proteins capable of producing false fixation with the active sera. Hence his results.

For the sake of clarity, I propose to call the non-specific reaction caused by active serum and these proteins *proteotropic fixation*, and the Wassermann reaction caused by syphilitic and leprous sera in the presence of lipoids *lipotropic.*

No parallelism is found to exist between the proteotropic and the lipotropic properties of a given specimen of serum. Inactivation removes the proteotropic property almost entirely, while it only reduces the lipotropic titre to about one-fourth of the original strength.

35 (445)

Experimental cirrhosis of the liver.

By **EUGENE L. OPIE.**

[*From the Laboratories of the Rockefeller Institute for Medical Research, New York.*]

Administration of chloroform by inhalation prolonged during one or more hours produces necrosis implicating the central part of the liver lobule. When recovery follows, connective tissue does not replace the destroyed parenchyma. By removing bits of liver tissue shortly after prolonged chloroform anesthesia Whipple has recently shown that necrosis destroying from one third to three fifths of the liver lobule rapidly undergoes repair so that at the end of three weeks the organ has returned to normal.

Herter and Williams have produced well marked cirrhosis by inhalation of chloroform repeated during several weeks. The following experiments are described because they show that advanced cirrhosis with portal obstruction may be produced in dogs by repeated administration of chloroform by mouth ; that two different lesions may be produced by the same substance.

One animal received thirty-three times 6.25 c.c. of chloroform in oil, doses being given on three succeeding days, followed by an interval of three days. The veins over the abdomen became markedly distended and there was jaundice. The animal died at the end of two months. The veins of the portal system were widely dilated, the mucous membrane of the intestinal tract was congested and the peritoneal cavity contained a small amount of fluid. The liver was small and mottled with yellow and gray. Microscopical examination shows that about one third of the liver substance consists of newly formed cellular connective tissue, in which are numerous proliferated bile ducts. The liver parenchyma is in process of regeneration ; mitotic figures occur and the columns of liver cells have assumed a tubular form with nuclei regularly arranged at the edges of the columns.

A second animal received twenty-one times 20 c.c. of chloroform. The doses were repeated on three succeeding days, followed by an interval of six days. The abdominal veins

became moderately distended and there was well-marked jaundice. The animal died at the end of two months. The peritoneal cavity contained a small amount of fluid. The liver was large and bright yellow. Microscopical examination showed advanced fatty degeneration with cirrhosis. Connective tissue, which is more sclerotic than in the former experiments, occupies about one third of the liver substance. The parenchyma shows advanced fatty degeneration, but little evidence of regeneration. Newly formed bile ducts are rare.

In other animals, which have received chloroform, dilatation of the superficial abdominal veins indicates the presence of hepatic cirrhosis.

36 (446)

Shaking experiments with protozoa.

By **MAX MORSE.**

[*From the Biological Laboratories of the College of the City of New York,*]

DeBary, Hofmeister, Horvath and Meltzer have observed that various species of lower plants (Myxomycetes, Diatoms, Oscillaria and Bacteria) when shaken, are brought to a quiescent condition, for a longer or shorter time or even killed. The present observations were based upon cultures of *Paramecium*, *Euglena*, *Stylonychia* and *Spirillum* (a species of Schizomycetes). Two methods of shaking were used: (1) Shaking was produced by means of a rotating arm moving in a radius of 25 cm. at a velocity varying from 66 to 83 revolutions per minute and carrying a tube, 6 cm. long within which was a phial holding 2.5 c.c. of the infusion of protozoa. During each revolution, consequently, the protozoa received two shocks from the falling of the smaller phial within the larger one. (2) Following the method of Horvath and adopted by Meltzer in his experiments, a horizontal shaker, making 100 excursions per minute through a path of 8.50 cm. was employed. A 250 c.c. bottle containing 10 c.c. of the infusion and bearing a pycnometer thermometer for registering temperature was fastened in the machine and another bottle similarly equipped was placed near as a check. The animals were shaken for from one to twenty-four hours.

Shaking for one hour in either machine showed little effect on any of the species, except that *Paramecium* became somewhat less active. With the horizontal shaker for a period of six hours, *Paramecium* and *Euglena* became sluggish and this sluggishness continued for several hours after removal from the machine. Twenty-four hour periods gave decided results, the two species just mentioned being either killed or rendered very sluggish. However, in all cases a few individuals were nearly normal. With *Stylonychia* and the bacterial species, *Spirillum*, the case was different inasmuch as no observable deviation from normal behavior was evident. The flattened shape of the former may have something to do with the results obtained with this form. The effects of shaking lasted for at least two weeks, during which period, there was a constantly decreasing number of individuals in the shaken cultures which were carefully compared with check experiments from "wild" forms and from the checks used with the experiment.

In order to test the hypothesis that shaking may increase or decrease the division rate in *Paramecium*, six individuals were isolated from the twenty-four hour cultures and their condition followed for seven days. During this period, the average rate of fission was approximately the same as that in the check forms.

That the sluggish movements were not the result of an emaciation due to lack of food, by the killing of bacteria, in shaking, which *Paramecium* uses for food, cultures were placed in sterile chambers immediately after their removal from the shaker. In such cases, no new bacteria were introduced. No difference was manifest from the control individuals.

Verworn, in commenting upon shaking experiments, suggests that the effect is that of establishing a tetanus in the organisms being experimented upon. That this explanation will scarcely hold in the present species is evident from the fact that as far as could be determined, the movements of the cilia and flagella were normal, or at least but slightly affected. If tetanus had set in, it is fair to assume that it would have reached the organs of locomotion as well as the body proper.

Metalnikoff, Mesnil, Moulton and others have demonstrated proteolytic, lipolytic and amylolytic enzymes in protozoa and the

suggestion is made that the effect of shaking is perhaps due to the destruction of these enzymes in the manner demonstrated for pepsin, trypsin and rennin by Meltzer and Shaklee and for tyrosinase and zymase by Abderhalden.

SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF THE COMMUNICATIONS.

Thirty seventh meeting.

The Rockefeller Institute for Medical Research. December 15, 1909. President Lee in the chair.

37 (447)

A new method for testing the interaction of ferments and anti-ferments.

By **S. FELDSTEIN** and **R. WEIL.**

[*From the Department of Experimental Therapeutics, Cornell Medical School.*]

Within the past two years, the antitryptic activity of human serum has been the subject of a considerable number of studies, and it has apparently become established that this property of the serum varies within wide limits in certain conditions of disease, being characteristically increased in all cachexias, notably so in cancer. Two methods have been employed in this study, which are exactly the same in principle, in that they are based on the use of a series of mixtures of trypsin in solution, and of the serum, the end-point in the one method being denoted by the smallest quantity of serum which totally inhibits the digestive action of the trypsin, on a plate of coagulated beef-serum, while, in the other, it is the lowest proportion of trypsin which completely digests the medium, namely, a solution of casein. It is evident that by either of these methods it is possible to determine only an approximate value of serum, lying between the two dilutions, just above and just below the so-called end-point. Moreover, the end-point itself is in neither method sharply defined. If, to these uncertainties, is added the fact that the media of digestion are subject to certain uncontrollable variations, such as the inherent differences in sera,— it will be

manifest that the methods are materially lacking in exactness. Consequently, the results have been divergent.

The viscosimeter * appears to offer a method which avoids these difficulties, and gives constant and reliable quantitive results. The viscosimeter is a capillary tube, as designed by Ostwald, on which there are two markings; the time is measured which is required by a solution to flow from the upper of these markings to the lower. Constant conditions of temperature are afforded by the use of a constant water bath with glass walls to permit the readings. A constant medium may be secured by making up a solution of the medium so as to run through the viscosimeter always in a definite space of time. For the purpose of testing tryptic digestion we have used solutions of gelatin. The delicacy of the method may be indicated by the following series of figures for variations of one tenth of one per cent. in the strength of the solution:

Normal salt solution,	70	seconds.
$\frac{1}{10}$ per cent. gelatin in above,	71	"
$\frac{2}{10}$ per cent. " " "	$72\frac{3}{5}$	"
$\frac{3}{10}$ per cent. " " "	$74\frac{3}{5}$	"
$\frac{4}{10}$ per cent. " " "	$75\frac{1}{5}$	"
$\frac{5}{10}$ per cent. " " "	$78\frac{3}{5}$	"
$\frac{6}{10}$ per cent. " " "	$80\frac{2}{5}$	"
$\frac{7}{10}$ per cent. " " "	$82\frac{2}{5}$	"
$\frac{8}{10}$ per cent. " " "	$83\frac{4}{5}$	"
$\frac{9}{10}$ per cent. " " "	$86\frac{4}{5}$	"
1 per cent. " " "	$89\frac{1}{5}$	"

It is evident that the greater the degree of digestion of the gelatin, the lower will be its viscosity and the lower the corresponding figures.

The accuracy with which the digestive action of varying amounts of the ferment upon gelatin may be determined, is indicated by the following series of figures, in which the differences are given for one hundredth of one per cent. of the trypsin, digestion having been interrupted at the end of one hour:

0.5 per cent. trypsin:	2	minutes,	51	seconds.
0.49 per cent. "	2	"	53	"
0.48 per cent. "	2	"	56	"

* The viscosimeter was first used in digestion experiments by Spriggs (*Zeit. f. physiol. Chemie*, 1902, XXXV., p. 480). Owing to the fact that he used a beef extract as his medium, the results were inconstant, and the method failed of any further application.

0.47 per cent.	"	2	"	58	"
0.46 per cent.	"	2	"	58	"
0.45 per cent.	"	3	"		
0.44 per cent.	"	3	"		
0.43 per cent.	"	3	"	02	"
0.42 per cent.	"	3	"	02	"
0.41 per cent.	"	3	"	04	"
0.4 per cent.	"	3	"	04	"

The accuracy with which the antitryptic value of serum can be determined, is illustrated by the following series of tests :

1 c.c. 1	per cent.	serum	+	1 c.c. 0.2	per cent.	trypsin,	1 min.	57	sec.	
1 c.c. 2	per cent.	"	+	1 c.c. 0.4	per cent.	"	1 "	58	"	
1 c.c. 1.5	per cent.	"	+	1 c.c. 0.2	per cent.	"	2 min.			
1 c.c. 3	per cent.	"	+	1 c.c. 0.4	per cent.	"	2 "			
1 c.c. 2	per cent.	"	+	1 c.c. 0.2	per cent.	"	2 "	2	"	
1 c.c. 4	per cent.	"	+	1 c.c. 0.4	per cent.	"	2 "	2	"	
1 c.c. 2.5	per cent.	"	+	1 c.c. 0.2	per cent.	"	2 "	4	"	
1 c.c. 5	per cent.	"	+	1 c.c. 0.4	per cent.	"	2 "	5	"	

Thus, it will be seen that the method permits of a very accurate estimation of the action of ferment at any given moment, and of the restraining action of anti-ferment, which can be progressively followed over considerable periods of time. It necessitates the use of only one dilution, instead of a series, as in previous methods. It determines the end-point exactly, instead of approximately. It determines variations in the media by means of the use of controls in each experiment, which is not possible by the methods now in use.

In testing human sera with a gelatin of an original viscosity time of four minutes, a trypsin of 0.5 per cent. strength and sera of 2 per cent. dilution, the range of inhibition covers approximately 60 seconds, so that the values of sera may be far more sharply differentiated than is possible with a series of five dilutions, as in the methods hitherto used.

We shall not give the details of the tests hitherto made, which embrace about two hundred sera of various conditions of disease. It is, however, worthy of emphasis, we believe, that the so-called anti-tryptic action of human sera manifests altogether different relative values when tested against the proteolytic ferment present in a glycerin extract of cancers as compared with the commercial trypsin derived from animals.

38 (448)

Resistance to the growth of cancer induced in rats by injection of autolyzed rat tissue.[1]

By **ISAAC LEVIN.**

[*From the Department of Pathology of Columbia University, at the College of Physicians and Surgeons.*]

It is a fairly well established fact that an immunity, or rather a resistance to the growth of a transplantable tumor may be induced in white mice and rats by artificial means. This acquired resistance is of a peculiar type and is not similar to the usual form of the anti-bacterial immunity. Clowes and Baeslack's assertion, that the serum of recovered mice cures cancer in other mice, has received no confirmation. Nor has any other known method of detecting the existence of immunity in an organism met with success in the animals refractory to growth of implanted cancer.

While the best manner of immunizing an animal against tumors consists in a previous unsuccessful inoculation of a tumor, this resistance does not appear to be specific. Ehrlich observed that an animal made resistant to a certain class of tumors, carcinoma for instance, is also resistant to the growth of an implantable sarcoma. Furthermore, a resistance may be artifically induced by previous inoculation of normal tissue of the same species of animals. Michaelis produced such an immunity by injection of normal mouse liver; Bashford by injection of blood or washed blood cells, but not by blood-serum; Schoene with different embryonic tissue; Bridré with liver and spleen.

All these methods of immunization seemed to be successful only when uninjured cells constitute a part of the substances used for the injections. Blood-serum, deprived of the cells, or normal or tumor tissue heated or crushed and frozen, does not induce any resistance — as was shown by the investigations of Michaelis and Haaland.

In view of all these facts, the opinion seems to prevail that an artificial immunity or resistance can only be induced by the inoc-

[1]This research is conducted at the expense of George Crocker Special Research Fund.

ulation of living tumor cells or of living normal cells. As Ehrlich puts it, we are dealing here with a cellular immunity, which consequently can only be caused by the live activities of the injected cells.

It has been shown by the investigations of Buchner, Salkowsky, M. Jacoby, P. A. Levene and others, that the majority of the so-called vital functions of the cell are produced by its endocellular enzymes. These enzymes, while constituting an integral component part of the cell, may remain under certain conditions uninjured after the death of the cell. The best method of liberating these endocellular enzymes consists in the autolysis of tissues.

It seemed feasible a priori that the resistance induced by normal mouse or rat tissue injected subcutaneously may also be due, not to the function of a live cell, but to some peculiar type of an endocellular ferment. With the aim in view to investigate this possibility, the present research was undertaken. The work was done with Ehrlich's sarcoma of a white rat, for a transplant of which the author is indebted to Dr. S. Flexner. This tumor is of a very malignant type and takes in from 100 per cent. to 80 per cent., grows to very large size, frequently gaining the size of two inches by one inch in about three weeks after inoculation. The tissue used for immunization was autolyzed liver of a "Nuller" — *i. e.*, a rat naturally resistant to sarcoma. Though resistance is induced by tissue of a normal animal, it was deemed advisable to enhance the chances for success by taking the tissue from a resistant animal. The liver was removed and kept under aseptic precautions at body temperature for two weeks; then the autolyzed liver tissue was mixed with about double the quantity of normal salt solution, ground thoroughly with sand, filtered, and 1 c.c. of the solution injected subcutaneously at different periods before or after the inoculation of the tumor. The rats used for the experiments were approximately of the same size and consequently of about the same age.

A diagram of the experiment follows (page 66).

The final examination and measurement of the tumors was done in about twenty-five days after inoculation, when the tumors reached already the highest point of growth. These results compare quite

	1	2	3	4	5	6	Total.	Control Rats.
Number of rats inoculated with tumor.	10	10	10	10	10	10	60	60
Number of rats survived at the final examination 25 days after inoculation.	5	10	10	10	6	10	51	57
Number of days *before* inoculation autolyzed liver injected.	10	5	3					
Number of days *after* inoculation autolyzed liver injected.				9	9	12		
Number of rats without growth or with small abortive nodules.	2	7	5	7	4	9	34	6
Number of rats with tumors.	3	3	5	3	2	1	17	51
Per cent. of takes.	60%	30%	50%	30%	33%	10%	34%	85%

favorably with the results obtained by L. Michaelis with the injection of liver emulsion, as is apparent from the second diagram, or

	Treated Animals.	Controls.
Number of mice inoculated with tumor	20	18
Number of mice without growth or with small stationary tumors	14	5
Number of mice with tumors	6	13
Per cent. of takes	30 per cent.	72 per cent.

even with Ehrlich's statement, that thirty mice immunized with a non-malignant hemorrhagic tumor took the subsequent inoculation of cancer in from 30 to 50 per cent., while the 30 control animals took in 100 per cent. Only Bridré claims to have obtained an absolute immunity with injection of normal spleen, but his conclusions are based on experiments on eight animals only.

It seems then possible to produce in rats a certain amount of resistance to growth of tumor by treatment with tissue, of which the cells are killed, but some endocellular enzyme-like substances may not have been injured in the process.

If we turn now to analyze the investigations of those who have worked with normal tissue, it seems feasible to interpret the results obtained by them in a similar way. It is hard to suppose that when a piece of tissue or an emulsion is injected under the skin, all the cells remain alive and are capable of normal function ten or twelve days later. It seems more probable that the majority of the cells die and undergo some changes similar to the autolytic

process. Very instructive in this connection is the work of Woglom. The spleen extirpated and then inoculated subcutaneously into the same animal induces resistance against growth of tumor. Extirpation of the spleen does not induce any resistance. If resistance is caused in this case by the live functions of the cells of the spleen, then they can act most effectively when the spleen is in situ, and the mice ought to have been naturally resistant. The explanation forces itself on one's mind that the spleen transferred under the skin is autolyzed or undergoes some other similar change.

That autolysis may be one of the means to which the organism resorts in order to elaborate protective substances, is shown by the very interesting investigations of Blum. He demonstrated that products of autolysis of normal tissue possess the power to neutralize tetanus and diphtheria toxins and cobra venom, and it is possible to save animals from death by injecting the products of autolysis subsequent to the injection of toxin.

This investigation is still in its beginning. Different tissues are tried and different methods employed to liberate the endocellular ferments. But the view-point, while new, seems to be correct and capable of stimulating further research, and it is therefore deemed advisable to give this short preliminary report of the present state of this investigation.

39 (449)

The inhibitory effect of magnesium upon indirect and direct irritability of frog muscle and the antagonistic action of sodium and calcium upon this effect.

By **DON R. JOSEPH** and **S. J. MELTZER.**

[*From the Department of Physiology and Pharmacology of the Laboratories of the Rockefeller Institute for Medical Research.*]

Several series of experiments were carried out on frogs. In the first series magnesium chloride was injected into a lymph sac and subsequently nerve and muscle were stimulated at various times by induction shocks. Of the results obtained two will be mentioned: One is that indirect irritability gradually disappeared completely while direct irritability remained practically unchanged,

that is, on stimulation of the nerve plexus there was no response while on stimulating the muscle directly there was a good contraction. Such a result was seen by many observers and was spoken of as curare-like action. In a previous paper we have called attention to the fact that similar results can be obtained also by *perfusion* of the leg with solutions of sodium chloride and even with calcium chloride. The magnesium effect, however, is somewhat more pronounced. The second result is that the subsequent infusion of the muscles through the abdominal aorta, with calcium chloride, restores rapidly the abolished indirect irritability. This is similar to the observation of Auer and Meltzer on the antagonistic action of calcium to magnesium in mammals and is also similar to the antagonistic action of calcium to the curare-like action of sodium chloride.

In another series of experiments the muscles of the leg of completely curarized frogs were perfused with magnesium chloride. There was, of course, on account of the curare, no indirect irritability from the start. In these experiments it was found as an invariable result that magnesium definitely abolished or reduced the direct irritability. There was then a definite difference with regard to the direct irritability between the action of magnesium and that of curare and the problem presented itself as to how to reconcile this experience with that of the first series of experiments in which the lymph sac injection of magnesium chloride had practically no effect upon the direct irritability of the muscle.

In the following series of experiments, however, facts came to light which are capable of explaining this apparent contradiction. In this series, legs of normal frogs were perfused with magnesium chloride through the aorta and were later perfused with calcium chloride and sodium chloride in various orders. The following results were obtained. In the first place, in all cases magnesium chloride reduced definitely or even completely abolished also the direct muscle irritability ; but this effect was somewhat slower and not as pronounced as the effect of the magnesium upon the indirect irritability. Furthermore, when after the depression caused by magnesium, calcium chloride was perfused, it caused no recovery either of the indirect or direct irritability. When instead of the calcium the perfusion of sodium chloride followed that of mag-

nesium the direct irritability soon returned, but not the indirect. However, when now the perfusion of calcium chloride followed, the indirect irritability recovered also and quite rapidly. The meaning of these experiments seems to be simply this: magnesium depresses the direct irritability as well as the indirect, the latter, however, somewhat more effectively than the former. Sodium restores the depressed direct irritability and when used alone, exerts no effect upon the indirect irritability. Calcium alone helps neither the direct nor indirect irritability but when it follows sodium (or when given with sodium) it restores promptly the indirect irritability. We can now interpret satisfactorily the results of the lymph sac injections. In these intact animals sodium chloride is present in sufficient quantity in the blood to prevent the depressing action of the magnesium upon the direct muscle irritability and, furthermore, the accumulated quantity of the sodium is still sufficient to assist the subsequent injection of the calcium in the restoration of the indirect irritability. In this connection we may also suggest further that even the striking antagonistic results obtained by Auer and Meltzer with calcium in mammals might not be due to the calcium alone but to the combination of the injected calcium plus the sodium present in the serum.

The last mentioned facts are an instructive example of the difference in the results obtained by injecting into an animal with intact circulation and by perfusion of bloodless organs, a difference which is not always kept in mind by many experimenters.

40 (450)

On the vaso-motor nerves of the stomach.

By **R. Burton-Opitz.**

[*From the Physiological Laboratory of Columbia University.*]

In order to demonstrate the existence of vaso-motor nerves in the stomach, the following method was resorted to: Quantitative measurements of the vascularity of the stomach were made by means of a stromuhr; while at the same time attempts were made to vary the normal bloodflow through this organ by means of stimulation of the splanchnic nerves.

The stromuhr was inserted in the vena gastro-lienalis between

the portal vein and the point of entrance of the vena gastrica dorsalis. The venous return from the spleen and pancreas was excluded from the stromuhr.

By stimulating the left splanchnic nerve, very marked reductions in the blood supply of the stomach were obtained. The curve recorded by the stromuhr under these conditions does not differ materially from the curves contained in earlier papers of the writer on the vaso-motor nerves of the spleen, intestine and kidney.

41 (451)

The change in the venous bloodflow on administration of amyl nitrite.

By **R. BURTON-OPITZ** and **H. F. WOLF.**

[*From the Physiological Laboratory of Columbia University.*]

Amyl nitrite was injected into the femoral artery, while the flow in the corresponding vein was being measured by a stromuhr. The resulting dilation of the capillaries betrayed itself by a marked increase in the flow and a corresponding rise in venous pressure. The arterial pressure recorded in the opposite femoral artery was not affected if the reaction remained confined to the area of the leg.

When the amyl nitrite was administered by inhalation or when the drug was injected into central venous channels, the venous bloodflow exhibited a decrease in accordance with the loss in arterial tonicity. The venous pressure did not undergo a material change during the period of arterial depression.

Inhalations of amyl nitrite were also resorted to, while the leg was being perfused with defibrinated blood. As in this case no alterations in the quantity of the perfusing liquid could be obtained, the experiment favors the view that amyl nitrite exerts a peripheral and not a central effect.

42 (452)

The fate of embryonic tissue implanted in the mother.

By **PEYTON ROUS.**

[*From the Laboratories of the Rockefeller Institute for Medical Research, New York.*]

The following experiments were done primarily to ascertain whether there exists, specific to the pregnant animal, a substance favoring the growth of embryonic tissue.

Many pregnant white mice were hysterectomized (leaving the ovaries *in situ*), and a measured portion of the hashed embryo implanted through a needle subcutaneously. The animals showed themselves only slightly susceptible to infection at operation, and in the great majority the laparotomy wound healed promptly and the general health remained good. It was found that the embryonic tissue grows profusely when implanted in the mother, yet not better than in certain unoperated, alien hosts. No evidence of a favoring substance specific to the pregnant animal was obtained.

In a number of experiments two mice were hysterectomized, and separate grafts of the hashed embryo from each were made in both, using the subcutaneous tissue of the flanks as the site of implantation. In general the embryonic material grew better in the animal that had furnished it,—a new demonstration of the importance of blood-relationship in transplantation.

It proved feasible to snare off from the forked uterus of the mouse one or more embryos, without damage to the others, which go on to term. The implanted material fails to grow in these mothers that still carry young. The contrast to what occurs in the completely hysterectomized mother, or in a favorable alien host, or, for that matter, in an unfavorable alien host is very striking.

As I have shown elsewhere,[1] individual mice differ much as hosts for the same hash of mouse-embryo. In some it is promptly vascularized and grows well, whereas in others no vascularization occurs and the fragments die within a few days. Histological examination shows that embryo implanted into the mother is

[1] *Jour. of Exper. Med.*, 1910, XII, No. 3.

vascularized; yet if she still carries young, it does not grow. On the other hand, it does not die, as it would in an unfavorable alien host. The fragments remain in good health for a considerable period. At the end of seven days the thin strand of grafted tissue consists of minute bits of cartilage, nests of epithelium, and a connective-tissue of embryonic type, all with little sign of degeneration; whereas in the hysterectomized mother the nodule that has already developed is made up of relatively large masses of cartilage, epithelial cysts distended with secretion or cast-off cells, and a connective tissue approaching the adult in type. Many signs of beginning degeneration are seen, in the cartilage especially.

These facts have a considerable bearing on tumor problems, especially on Ehrlich's hypothesis of immunity by atrepsia — immunity by the lack of a specific food substance. Ehrlich holds that a specific "X substance" is necessary to tumor growth because (1) mouse tumor when introduced into rats grows for a short period only and then retrogresses, — presumably for lack of the "X substance," and (2) because the presence of a large, rapidly growing tumor in a mouse prevents (by its utilization of "X substance") the development of other grafts in the same animal. But in view of the experiments just detailed, it must be granted that, if tumor requires an "X substance," so developing embryo requires a "Y substance." For (1) mouse embryo when implanted in rats grows for a brief period and then retrogresses,[2] and (2) the presence of a developing litter *in utero* prevents the growth of embryo grafts.

But the question may well be asked whether one need suppose for the growth of tumor or embryo the presence of special substances other than the circulating food required by mouse-tissue in general. A lack of this might well explain the ultimate failure of grafts in the rat, and its total utilization this failure when the host-mouse already carries a rapidly growing tumor or a litter of developing embryos. It should also be recalled that numerous observers have found pregnancy of the host to interfere with the growth of implanted tumors.

[2] *Loc. cit.*

43 (453)

The behavior of transplanted mixtures of tumor and embryo.

By **PEYTON ROUS.**

[*From the Laboratories of the Rockefeller Institute for Medical Research, New York.*]

Mixtures of hashed mouse-embryo and transplantable mouse-tumor were inoculated into the subcutaneous tissue of adult animals. It was found that growth of both elements took place, often in intimate association. But to obtain these results a balancing of avidity was necessary, such as Apolant used in his mixtures of sarcoma and carcinoma. Only tumor-cells of sluggish character can be implanted with the embryonic cells, which otherwise are outgrown and soon die. This is interesting in view of the enormous proliferative ability of the embryonic cells *in utero*, and it would seem to show that such ability depends at least as much on the excellent nutritive arrangement *in utero* as on inherent cell-energy. The transplanted cells not only lack the power of unlimited growth that characterizes tumor, but during their temporary growth in a new environment lack the proliferative energy that many tumors show.

In a mixed graft that has only partially succeeded, tumor and embryo tend to grow or fail together. This must be largely a matter of immediate nutritive conditions, which are best, for example, at the edge of the graft. But it is also notable that at those points where one element has elicited a supporting reaction from the host tissues and is growing, the other has also succeeded. When the tumor mass is walled off from the host by a layer of developing embryo, it nevertheless grows, utilizing as stroma the embryonic connective tissue.

In a number of quantitative experiments it was found that tumor and embryo succeed better alone than when mixed. This difference is at first not marked. Later, when the embryonic element of the mixed graft, after its short period of development, breaks down, more or less of the tumor is involved with it.

It was observed not infrequently that the embryonic epithelium and the carcinomata united when they met during the process

of growth, and this though the one was squamous in type, the other adenomatous. So perfect was the apposition of cells that but for the sharp transition from one tissue to another, an observer in ignorance of the conditions of experiment could well believe that here had occurred a metaplasia. The fact thus experimentally proven that cancerous and normal epithelium can secondarily unite must not be forgotten in judging instances of apparent metaplasia at the edge of tumors.

44 (454)

Vaughan's split products and unbroken proteins. A comparative study of their effects.

By **EDWIN J. BANZHAF** and **EDNA STEINHARDT.**

[*From the Research Laboratory, Department of Health, New York City.*]

The following is a brief summary of our results:

Comparing the Action of Vaughan's Egg-white Poison to Unbroken Protein.

1. Inoculations of the unneutralized acid poison into normal guinea pigs gave the same picture as that of the unbroken protein when inoculated into sensitized guinea pigs, whether the poison was given intraperitoneally or intracerebrally. The filtrate from the neutralized poison injected intracardiacally also gave typical symptoms.

2. *Effect of Heat.* — The egg-white poison was not affected when heated to 100° C. for 15 minutes; heated to 120° C. for 15 minutes it was reduced, but its toxic action not completely destroyed.

3. *Chloral Hydrate.* — Normal guinea pigs under the influence of chloral were completely protected against one and a quarter fatal doses of the poison. If two or more fatal doses are given death results. Chloral mixed with the poison, and then given, caused irregular results which was interpreted as meaning that there is no chemical union of the chloral and poison *in vitro.* We assume that the chloral protects by union with certain vital cells.

4. *Lecithin (Egg) Effect on Serum Anaphylaxis.* — Emulsified with the serum and the resulting emulsion injected into serum

sensitized guinea pigs, no protection resulted. Lecithin given, in doses from 250 to 500 milligrams or more, to serum sensitized guinea pigs protects them from a second injection of 5 c.c. horse serum given twenty hours later.

Lecithin (Egg) Effect on the Poison.

Neither when emulsified with the poison; nor given as a preliminary injection, followed by the egg-white poison, twenty hours later, was there any protection afforded. The difference in the protective action of preliminary doses with the serum and with the poison, we think, is due to the absorption by the lecithin of the ferment in the sensitized guinea pig which causes the splitting of the whole protein, thus preventing the cleavage and liberation of the poison.

In the case of the poison, this cleavage has been done in the retort, and as the lecithin does not protect against the poison itself, death occurs as in control animals. Apparently this supposed absorption of ferment by the lecithin takes place slowly for if the lecithin and serum are injected simultaneously death occurs typically.

Eighteen to one hundred hours after the inoculation of 500 milligrams of lecithin the serum sensitized animals were protected from the second injection of 5 c.c. horse serum. Thus far these are the time limits, after the injection of lecithin, that we have allowed before giving the second injection.

We assume, with Banzhaf and Famulener, that chloral allows the ferment or zymogen in a sensitized guinea pig to split the protein, but protects the animal's vital cells from the action of the poison, and similarly protects the normal guinea pig from Vaughan's split poison.

The Residue.

1. The sensitizing action of Vaughan's residue (egg-white) differs with different products. Two out of three were inactive. This inactivity may be due to the heat used in the Vaughan method. In fact the loss of the toxic properties of the residue can be fully explained through the action of the heat alone, irrespective of any cleavage of the molecule due to the alcohol and sodium hydroxide used.

2. All vaccinating properties of the active egg-white residue appears to be completely absent. This, also, would be expected from the prolonged heating to which it has been subjected, which is in complete accord with the effect of heat on whole protein.

The toxic and vaccinating properties are first lost and, later, the sensitizing properties. The finding of the residues incapable of sensitizing completes the parallel of the effect of heat on unbroken proteins.

If the vaccinating properties of the typhoid residue are lost, as might be inferred from the loss of those of the egg-white, the use of large doses of the typhoid residue to absorb the bacteriolytic ferment in typhoid fever showing severe toxic symptoms, as suggested by Vaughan, would probably not be successful. Experiments now being carried out on the typhoid residue, will, we hope, soon permit us to make a definite statement on this point.

3. *Besredka's Antianaphylactic Vaccination.*— Following the method of Besredka, precipitating serum protein with alcohol and extracting the precipitate with physiological salt solution, a filtrate was obtained, called by him "petit serum." According to his article this "petit serum" was never toxic to a serum sensitized guinea pig, and yet it vaccinated, but did not sensitize. Proceeding on the theory that Besredka's results were due to the dilution of this protein, not to a separation of the substances, we concentrated the filtrate of his "petit serum." On intracardiac injection five out of seven serum sensitized guinea pigs gave typical anaphylactic symptoms, followed by death. This proves that the lack of toxicity in his work had been due to dilution and not to freedom from the substance producing toxic substances.

The sensitizing action was tested out, and in certain doses we were able to sensitize animals, not as regularly as with whole serum, but sufficiently to show the presence of sensitizing properties in the "petit serum."

4. *Absence of Antianaphylaxis in Rabbits*— In conclusion we wish to confirm the results of Arthus, Lesué, and Dreyfus, that antianaphylaxis is not produced in the rabbit by the methods that ordinarily so readily and rapidly produce it in the guinea pig.

The present attitude of comparing man's sensibility to serum with that of the guinea pig is possibly an error. Man, perhaps,

should rather be compared to the rabbit. The rabbit does not show the explosive anaphylaxis of the guinea pig, unless the inoculation is given intravenously. The occurrence of this in man is rare and under conditions not yet understood and not explainable by the guinea pig. This occurrence is occasionally shown after the first injection of serum.

The ordinary serum sickness in man is not grave, nor need the Arthus phenomenon in the rabbit be grave. Therefore, any attempts at finding a method of antianaphylaxis which does not resensitize, for practical purposes, in man should be tried out in the rabbit as well as the guinea pig.

We wish to thank Dr. Vaughan for his generosity and kindness in sending us his split products, and for his courtesy in permitting one of us to finish our work in his own laboratory.

45 (455)

Notes on sensitization with tuberculin to tubercular rabbit-serum.[1]

By **J. P. ATKINSON** and **C. B. FITZPATRICK.**

[*From the Chemical and Research Laboratories, Department of Health, New York City.*]

These notes are some of the results of our study of sera, toxins and related substances. We have noted by means of the kymograph the changes in pressure and respiration produced when we injected into normal dogs, treated with tuberculin or other toxic substances, the sera of normal and diseased animals. A number of interesting facts were found in this way, regarding substances in the serum of animals having tuberculosis, which we think worth reporting.

The tubercular rabbit serum with which these results were obtained, was drawn from rabbits which had been infected 35 days previously with a virulent culture of bovine tuberculosis injected intravenously. The serum was defibrinated and separated centrifugally.

[1] This paper was presented by title at the meeting of the American Association for the Advancement of Science, Dec. 27, 1909.

We obtained the described reactions with the serum both before and after filtration, through a Berkefeld filter. The serum which was employed the day after drawing gave the reaction, and serum, after standing in the ice-box for ten days, also gave it. The same serum after three weeks did not give the reaction (protocol, Dec. 22, 1909).

The anesthetic used consisted of 10 mgs. of morphine sulphate followed in about thirty minutes by 1.5 gms. of chloretone and a little ether. The animals used were dogs averaging thirty pounds in weight.

The results obtained are summarized as follows:

1. Dogs injected intravenously with 3 c.c. of serum from a rabbit infected with tuberculosis do not suffer a reduction in arterial pressure. The serum was injected into the femoral vein and pressure taken in the carotid (protocol of Nov. 17, 1909).

2. Dogs that have been injected intravenously with 5 c.c. of crude tuberculin and five minutes later with 3 c.c. of serum (administered in the same way), which had been obtained from a tubercular rabbit do not suffer a reduction in arterial pressure. The same is true when the serum is administered first and then the tuberculin five minutes later (protocol of Nov. 17, 1909).

3. Dogs sensitized by a subcutaneous injection of 5 c.c. of tuberculin, which is followed in from twelve to eighteen hours by an intravenous injection of 1.5 to 3 c.c. of tubercular rabbit serum *do suffer a marked reduction in arterial pressure.*

4. This reaction is specific as far as we have been able to test it (protocol of Dec. 4, 1909). The following sera have been tested: glanders (horse), typhoid (human), antityphoid (horse), antistreptococcus (horse) normal rabbit, normal horse and a two per cent. solution of Witte's peptone. We have one record showing that the 5 weeks' old tubercular rabbit serum which did not cause the reaction in a sensitized dog, was reactivated by the addition of an equal amount of fresh rabbit serum.

5. Based on this reaction an attempt was made to immunize two rabbits against tuberculosis without success. The rabbits were injected with one cubic centimeter of the crude tuberculin and beginning upon the next day received 2 c.c. of the tuberculosis serum on alternate days during a period of ten days.

Each rabbit received five injections of the tuberculosis serum of 5 c.c. each.

The subcutaneous injection of 10 c.c. of the tuberculosis serum into three rabbits, each of which had been previously sensitized by an injection of 1 c.c. of crude tuberculin, caused death in from 24 to 50 hours.

6. This reaction, if found to be sufficiently specific, may be used as another method for the diagnosis of tuberculosis. This test would be made on an animal sensitized with tuberculin, by an injection of the patient's blood-serum.

7. We have obtained in normal dogs, by the intravenous injection of 4 c.c. of serum from rabbits in the paralytic stage of hydrophobia (seventh day after subdural inoculation), a marked depression in the arterial blood pressure. A similar reaction was caused by the intravenous injection of a substance (probably cholin), in small doses, obtained from the brains of calves and rabbits.

8. We made the following experiments, in order to ascertain what relation this reaction (see paragraph 3 above) has to anaphylaxis, as we now know it. Five dogs were employed. Dog No. 1 received a subcutaneous injection of 2 c.c. of normal horse serum. No. 2 received 1/75 c.c. No. 3 received 1/100 c.c. No. 4 received 1/1,000 c.c. No. 5 received two injections of 1/10,000 with an interval of four days between the injections. None of these dogs gave a reaction which could be recorded on the kymograph, when given intravenously on the following day 10 c.c. of the same normal horse serum. These results apparently indicate that the reaction is simply one of the many phases of sensitization or increased susceptibility, following the action of toxic substances. It resembles then the anaphylactic reaction only to this extent, namely, that although differing from one another, each is simply one of the many phases of increased susceptibility. We have tentatively named the phenomenon observed by us, vasophylaxis.

We desire to thank Dr. Wm. H. Park, Director of the Research Laboratory, Department of Health, New York City, for his kindness in furnishing us material for these experiments.

46 (456)

Remote results of the replantation of the kidneys.

By **ALEXIS CARREL.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

When a kidney is extirpated from an animal and replanted on the same animal with a proper technique, it does not undergo any anatomical or physiological changes. In several cases, I examined a kidney several months after its extirpation and replantation and could not detect any anatomical change. Ten months after the resection and the replantation of the left kidney of a dog, the organ was examined. Its size and appearance were identical to those of the right kidney. The vascular and ureteral anastomosis were almost invisible. There were no microscopical differences between the kidneys.

Two years ago, a bitch underwent a double nephrectomy and the replantation of the left kidney. Since that time she has become pregnant twice, has had a number of normal pups, and is still in perfect health.

These experiments show that, from a surgical standpoint, the question of the graft of organs is solved. The bad results obtained by some experimenters are due merely to faults of technique.

47 (457)

Temporary diversion from the left ventricle to the descending aorta.

By **ALEXIS CARREL.**

In the plastic operations on the thoracic aorta, it is necessary not to interrupt the circulation for a long time. Therefore, the blood must be diverted. I described already the central diversion of the blood by intubation of the aorta. I attempted also to established a communication between the left ventricle and the descending aorta, by means of a paraffined rubber tube or a vein preserved in cold storage. I succeeded twice to direct the blood directly from the heart into the descending aorta. The ascending aorta was then clamped, and the circulation reversed through the upper part of the descending aorta.

The purpose of these experiments is to develop a technique permitting operations on the first part of the arch of the aorta.

48 (458)

Remote results of the replantation of the spleen.

By **ALEXIS CARREL.**

On February 24, 1908, the spleen of a large dog was extirpated, then replanted and the circulation reëstablished after an interruption of forty-four minutes. On June 21, 1909, the abdomen was reopened and the spleen found normal. The dog was in excellent health. On November 1, 1909, the animal died at the farm. The spleen was normal from a microscopical and macroscopical standpoint. The anastomoses of the vessels were almost invisible.

This experiment shows that a spleen extirpated and replanted remains in normal condition for more than twenty months after the operation.

49 (459)

The mechanism of the depressor action of dog's urine with some observations on the antagonistic action of adrenalin.

By **RICHARD M. PEARCE** and **ARTHUR B. EISENBREY.**

[*From the Carnegie Laboratory of New York University.*]

Summary. — The intravenous injections of dog's urine into the dog causes an abrupt but transient lowering of blood pressure, varying from 20 to 90 mm. Hg (usually 40 to 70), not accompanied by disturbance of heart action and with little respiratory disturbance. Section of the spinal cord, vagi, cervical sympathetic and splanchnic nerves and destruction of cœliac ganglia and solar plexus individually or collectively does not abolish the depressor action. Physiological and pharmacological experiments based on Dixon's studies of the action of apocodeine show that when the nerve endings are so paralyzed by apocodeine that adrenalin causes little or no reaction, the urine also has no effect. Likewise, in normal animals, and in those with central vaso-motor influence eliminated, the action of urine is antagonistic to that of adrenalin and barium and during the increased pressure due to electrical stimu-

lation of the nerves of the splanchnic area, the urine causes a fall in pressure.

From these observations it is concluded that the urine lowers pressure through its paralyzing effect on the endings of the vasomotor nerves.

Dog's urine in doses of three cubic centimeters given intravenously may be used in physiological and pharmacological experiments to produce an abrupt and marked but transient fall in pressure with no secondary effect, in the same way that adrenalin is used to produce a corresponding rise in pressure.

The physiological antagonism between urine and adrenalin, which evidently act on the same anatomical structures, suggests the possibility that the depressor substance of urine represents a body which previous to its elimination may have a regulatory influence on the circulation directly opposed to that of the secretion of the adrenal gland.

(50) 460

On the elimination of bacteria from the blood through the wall of the intestine.

By **ALFRED F. HESS, M.D.**

Last year in a paper presented before this Society on, "Antiperistalsis in its relation to tubercle bacilli and other bacteria in the alimentary tract," I noted that bacteria which are injected into the blood current of rabbits could be recovered by culture from the contents of the small intestine. Since then I have followed this problem further, investigating the path by which the bacteria enter the alimentary tract, and, although the work is not completed, I have arrived at certain definite conclusions.

It has been shown by previous workers that some soluble poisons, notably morphine and snake venom, are excreted from the blood through the stomach. It has likewise been demonstrated that various salts, mainly soluble salts, such as strontium or lithium chloride, may be found in the intestine following intravenous injection. It is most probable that the authors of these experiments are correct in deducing that these salts have traversed the wall of the intestine; however, it should be noted, that in none of these

experiments was the common bile duct or pancreatic duct ligated, and entrance to the gut by this route excluded.

For almost all our experiments rabbits were employed. The test bacterium was *Bacillus prodigiosus*, which unless otherwise stated, was suspended in 0.8 per cent. salt solution and inoculated into the ear vein. After two experiments had shown that the injected bacteria were to be found in the small intestine, further experiments were undertaken to discover their portal of entry. Four routes seemed possible: (1) the bacteria may enter the lung and then gain access to the gastro-intestinal tract; (2) they may enter the intestine through the common bile duct or (3) through the pancreatic duct, or (4) traverse the wall of the intestine. Experiments were undertaken to discover whether this last route was possible, and to this end the other paths were one by one excluded.

In two experiments the pylorus was ligated in order to exclude the possibility of bacteria descending from the respiratory tract. As in all the experiments the inoculation of test bacteria was not made until the animal had recovered from the shock of the operation, which interval was generally one to two hours. After the inoculation the animal was killed in from one to three hours. Cultures were then made from different levels of the gut, under the precautions as to sterility which I have mentioned in my previous paper. Varying amounts of the contents of the intestine were used for culture, from one platinum loop of 4 mm. diameter to 1 c.c.; this was transferred to large tubes of broth, from which in turn agar plates were made. In some instances forty to fifty broth tubes were inoculated. In these preliminary experiments, in which the pylorus was ligated, it was proved that if three loops of agar culture of *Bacillus prodigiosus* were inoculated, this bacillus could be recovered from the small intestine two and one half hours later.

Of three experiments in which the common bile duct was ligated, two gave positive results. The smallest amount of culture employed was two platinum loops. *Bacillus prodigiosus* could not be recovered from the stomach, but was present in large numbers in the bile. In one of these experiments rabbits' serum was used as a menstruum instead of salt solution.

In five experiments the pancreatic duct as well as the com-

mon bile duct was ligated or also incised. In rabbits this is very easy to carry out, as the pancreatic duct enters the intestine separately and many inches below the bile duct. All five experiments gave positive results. The smallest amount injected was one loop of culture, which was recovered after the animal had lived for one hour.

In order to prevent the damming back of the bile, consequent to ligation of the common duct, two experiments, in which the duct was not obstructed, were undertaken. In these the duodenum was ligated and divided in its upper part, so that the bile flowed freely into its upper segment and no stagnation ensued. In addition the pancreatic duct was ligated. In one of these experiments in which one loop of culture was inoculated, *Bacillus prodigiosus* was recovered from the lower duodenum and the ileum.

Finally a dog was experimented upon. A duodenal fistula was made, the upper segment of gut including the openings of the pancreatic and the bile ducts. After the upper end of the duodenum was closed off, four loops of culture suspended in 4 c.c. of salt solution were injected into the jugular vein, the animal having been starved previously for twenty-four hours. Two hours later *Bacillus prodigiosus* was recovered from the lower segment of the small intestine, the gall bladder, and the urine, but not from the cecum or large intestine.

In some of this series of experiments the small intestine was ligated so as to divide it into sections, to see whether we could determine whether there was any difference as regards the permeability of the various segments of the gut. We found, however, that all parts of the small intestine acted alike in this respect.

It is very difficult to estimate even approximately the number of bacteria that may traverse the intestinal wall in this way. In general it may be said that in rabbits using an inoculation of one to three loops of culture material, not a very large number of organisms seem to be excreted by this route, as they could not be cultivated regularly from each tube, even though one half to one cubic centimeter of the intestinal contents was used for culture purpose. In the small intestine and especially in the duodenum the living bacteria are normally so few that large amounts of the fecal contents can be used for culture without danger of losing

sight of the test organism. It was found that the bacteria were excreted in large numbers by the bile. They were also found to a less degree in the urine; however, no extended quantitative estimations were made in this regard.

We have not been able to demonstrate the way by which the bacteria pass from the blood or lymph through the intestinal mucosa; whether unaided or with the help of the leucocytes. The experiments are being continued in this direction.

51 (461)

A report on the production of tabardillo, or Mexican typhus fever, in monkeys.

By **JOHN F. ANDERSON**, *Director Hygienic Laboratory, and* **JOSEPH GOLDBERGER**, *Passed Assistant Surgeon, U. S. Public Health and Marine-Hospital Service, Washington, D. C.*

It has been found that at least two species of monkeys, the *Macacus rhesus* and *Cebus capuchinus*, are susceptible to infection with tabardillo or Mexican typhus fever by direct inoculation with blood from human cases of this disease.[1] An attack of the disease in the monkey, produced by blood inoculation directly from man, induces a definite immunity to a subsequent inoculation with virulent blood.[2] Two monkeys, one a *rhesus* and the other a *capuchinus*, which were tested for their immunity 23 and 30 days respectively after the subsidence of their fever, were found to be immune to inoculation with large doses of virulent blood. Some of the same blood inoculated into two untreated monkeys produced, after an incubation period of eight days, a febrile curve similar to that of human cases of tabardillo. Blood taken from one of these animals on the sixth day of the fever and used for passage into another monkey, caused, after an incubation period of seven days, a similar febrile curve.

The blood of a *Macacus rhesus* infected from a human case

[1] Anderson, John F., and Goldberger, Joseph, A note on the etiology of "tabardillo," the typhus fever of Mexico. Public Health Reports, Dec. 24, 1909, XXIV, 1941.

[2] Anderson, John F., and Goldberger, Joseph, On the infectivity of tabardillo, or Mexican typhus, for monkeys and studies on its mode of transmission. Public Health Reports, Feb. 18, 1910, XXV.

was found to be infective for other monkeys on the fifth and sixth days of illness.

Diluted blood serum from a human case of tabardillo was passed through a Berkefeld filter, but failed when inoculated into a *Macacus rhesus* to cause any reaction. It would seem, therefore, that either the infecting agent was too small to pass through a Berkefeld filter or passed through in insufficient quantities to produce the disease.

The epidemiological evidence, supported by one human experiment, indicates very strongly that Mexican typhus fever is not contagious in the usual sense of the word. An intermediary host is probably the means by which the disease is transmitted from person to person, and the probable insect concerned is the body louse, *Pediculus vestimenti.*

The non-identity of the Mexican typhus fever and the Rocky Mountain spotted fever, which prevail at approximately the same altitudes, was demonstrated by animal inoculation as well as by the observation of certain important clinical differences.[1]

[1] Anderson, John F., and Goldberger, Joseph, On the relation of Rocky Mountain spotted fever to the typhus fever of Mexico. A preliminary note. Public Heath Reports, Dec. 10, 1909, XXIV, 1861.

SCIENTIFIC PROCEEDINGS.

Abstracts of the Communications.

Thirty eighth meeting.

Cornell University Medical College. April 20, 1910. President Morgan in the chair.

52 (462)

On the neurocytologic changes in shock, infection, Graves' disease, and certain drugs, with a note on fear in rabbits.

By **George W. Crile, M.D.**

In a series of observations on the neurocytes of the cortex, the cerebellum and the medulla in shock, infection, Graves' disease, iodoform, strychnia and alcohol poisoning, these cells, principally in the fatal cases, showed a marked alteration in the nucleus-plasma relation and in the size of the cell.

In the infections, in Graves' disease, in iodoform poisoning and in shock, these changes while varying greatly were in some degree seen in most of the cells. In alcohol and strychnia poisoning some cells were extremely altered while others were but slightly or not at all changed. The changes were studied by counting and measurement and compared with the normal. Due allowance was made for the great variation in the normal. A study of a large series of normal animals served as a basis for comparison. For example, in the normal no cell showing destruction of the nucleus and nucleolus with rupture of the cell membrane was observed, while in the fatal cases from the various diseases studied, there were many such cells. The tissue was all taken fresh, much of it was taken during life and dropped immediately in the fixative solution.

Frightened rabbits subjected to no trauma and no exercise showed almost complete prostration. Their brains in contrast

with normal animals took a much deeper Nissl stain and showed a disturbance of the nucleus-plasma relation and size of the cells.

53 (463)

Further observations on hemolysis in cancer.

By **GEORGE W. CRILE, M.D.**

This note is based on a study of fifty-two cases. Blood from three normal individuals is used for each test. With each there is a control heated to 55° C. for ten minutes and also a salt control. A hemolytic reaction in one or more tubes is counted as a positive test. Of the cases offering a fair surgical risk, 82 per cent. showed a positive reaction; of the advanced cases 39 per cent. showed reaction. Of these all but one showed reverse hemolysis. These results conform with my former tables. The total number thus far observed is three hundred and one. In a large number of observations upon surgical patients other than those with cancer or tuberculosis, there is rarely a hemolytic reaction. In tuberculosis the reaction, when present, is always reverse. In chronic infection there is, in about ten per cent., a direct hemolysis. Among apparently normal individuals, hemolysis occurs in about two per cent.

We conclude that hemolysis occurs rarely in normal individuals, occasionally in routine surgical patients excepting those with tuberculosis and cancer. In active tuberculosis it is the rule and is always of the reverse type. In advanced cancer there is hemolysis in about two out of five patients and in these the hemolysis is usually reverse. In the operable stage of cancer among about four out of five patients direct hemolysis occurs. Hemolysis is therefore additional evidence of cancer, but in no sense specific.

54 (464)

On the behavior of autodermic and isodermic skin grafts in cancer.

By **GEORGE W. CRILE, M.D.**

I have observed in cases having growing cancers that isodermic grafts of skin from husband and from son caused a marked local reaction, characterized by excessive exudation, edema, red-

ness and finally by the complete break-down of the grafts, while autodermic grafting later was entirely successful.

Tests in other cases were made by applying a single isograft alongside of autografts. In the cases thus far known to have at the time growing cancer, the isografts did not live. In other cases, we have not yet the final data. Histologic studies showed degeneration of the deeper cellular elements of the isografts. Nine cases were thus observed.

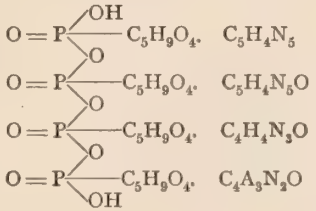
55 (465)

On yeast nucleic acid.

By **P. A. Levene** and **W. A. Jacobs.**

[*From the Department of Chemistry of the Laboratories of the Rockefeller Institute for Medical Research.*]

On hydrolysis of yeast nucleic acid the following components had been maintained: adenin, guanin, cytosin, uracil, dribose and phosphoric acid. On the basis of this knowledge and on the basis of the results of the elementary composition of the acid, the composition of the yeast nucleic acid was expressed schematically in the following manner:



That part of this assumption which tended to give expression to the manner in which the purin bases were linked in the molecule was confirmed by the finding of two ribosides, namely, guanosin and adenosin. However, there are known some properties of the nucleic acid which cannot be well interpreted by assuming for the pyrimidin bases the same manner of union as for the purin bases.

A new substance was obtained on hydrolysis of the yeast nucleic acid of the composition of $C_5H_9O_4C_4H_4N_3O$. On hydrolysis the substance yields cytosin, but no ribose. It contains in its molecule one free amino group and two hydroxyls. The following crystalline derivatives of the substance were obtained: picrate

sulphate, hydrochloride, tribenzoyl-derivative. The free substance and the salts are dextrorotatory. On the basis of this it is assumed that the new substance is a complex of cytosin and of a substance which is not a pentose. This necessitates the modification of that part of the formula of the yeast nucleic acid which gives expression to the form of the union of the pyrimidin bases in the molecule.

The new assumption is in harmony with all the properties of the nucleic acid; it also is in harmony with the fact that on distillation of the nucleic acid with hydrochloric acid an amount of furfurol was obtained which corresponded not to 44 per cent. of pentose (as the old formula requires) but to about 25 per cent., which is the required proportion by the modified formula.

56 (466)

The reaction of the uterine mucosa towards foreign bodies introduced into the uterine cavity.

By **LEO LOEB.**

[*From the Laboratory of Experimental Pathology of the University of Pennsylvania.*

I found that the introduction of foreign bodies into the uterine cavity approximately six days after ovulation leads to a rapid transformation of the whole uterine mucosa of the guinea-pig into a maternal placenta. Within 5 or 6 days an extraordinary increase in the size of the uterus takes place; this is followed by a period in which the pressure upon the newly formed placental tissue enclosed within the uterine muscle wall becomes so great that autolysis sets in and within a few days most of the placental tissue has been transformed into a brownish fluid.

In these experiments no ovum had previously entered the uterine cavity, the Fallopian tubes having been ligatured very soon after copulation in each case. The introduction of small particles of paraffin, of a very thin glass rod, of the thinnest platinum wire will serve for this purpose; since the latter, however, is only in partial contact with the uterine mucosa, it is not as effective as the glass rod or the paraffin. These foreign bodies do not act by separating the constituents of the uterine mucosa, that is, by

removing the lateral tissue tension ; investigations which are under way at the present time will show whether or not they exert an injurious influence upon the surface epithelium. Foreign bodies in combination with a specific substance carried to the connective tissue cells exert therefore a formative stimulus of extraordinary intensity. It would be premature to connect these facts in any definite manner with hypotheses which have been put forward in order to explain cell division (as for instance, changes in surface tension caused by changes in the permeability of the cell membranes). If we consider that, as I have previously shown, an apparently identical combination of stimuli acts in a specifically different manner upon the uterine mucosa of the rabbit and of the guinea-pig, the difficulty of such an undertaking becomes apparent. Concerning the rôle played by the ovum in the formation of the placenta, we may conclude from these experiments that it is purely mechanical and that it can be imitated by the contact action of non-specific foreign bodies. The quantity of newly formed placenta is, however, much greater under the influence of the foreign body, because the latter comes into contact with a much larger area of the mucosa, the influence of the ovum being considerably more localized.

57 (467)

The adsorption of the venom of Heloderma suspectum.[1]

By **LEO LOEB** and **MOYER S. FLEISHER.**

[*From the Laboratory of Experimental Pathology of the University of Pennsylvania.*]

Heloderma suspectum is naturally immune against subcutaneous injection of its own venom. We endeavored to contribute to an analysis of the mechanism of this immunity through a study of the conditions that determine the fixation of the venom by suspension of various organs and of inorganic and organic substances *in vitro.* Such investigations also promised to become of importance for an understanding of the difference in the toxic action of the venom in various animals. The following are the principal results we obtained.

1. Carmine and charcoal both adsorb a relatively large quan-

[1] This investigation has been conducted under a grant from the Carnegie Institution.

tity of venom, but comparing the adsorbing power of equal volumes of carmine and charcoal, charcoal is found to adsorb considerably more venom than carmine. The fixation of venom on charcoal is very strong and no dissociation of the adsorbed substance is found to take place after injection of the charcoal containing the adsorbed venom into the animal body. Addition of a small amount of weak acid to the venom-charcoal mixture does not influence markedly the adsorption process, while addition of alkali interferes with the adsorption, diminishing the quantity of the adsorbed venom, and causing the adsorption to be less firm. The addition of blood serum of the rabbit or dog also reduces markedly the adsorption of venom, while lecithin does not influence adsorption of venom by charcoal. Kaolin adsorbs considerable quantities of venom but less than charcoal, and the union between kaolin and the venom is easily broken up, when the mixture is injected into the body. Aluminium oxide, if free from alkali, adsorbs a large quantity of venom, but the combination is a loose one and is easily broken up in the body. Emulsified olive oil does not adsorb any venom. Lecithin adsorbs a definite but not very large proportion of venom. Filtration of venom through a Berkefeld filter is necessary in order to free after previous centrifugation the supernatant fluid from fine particles of lecithin that had adsorbed a certain quantity of the venom. Lecithin adsorbs considerably less than charcoal. After injection into the animal body dissociation of the venom takes place very readily. Addition of cholesterin to lecithin causes an additional adsorption of venom, but in this case also the combination is a very loose one.

Adsorbing Power of the Organs of various Animals for the Venom of Heloderma. — As in the case of adsorbing substances mentioned above the degree of adsorption of the venom by suspension of organs was tested by injecting the supernatant fluid as well as the residue. Only in a few cases filtration through a Berkefeld filter was made use of. Usually brain, liver, kidney, in some cases also ova, erythrocytes and blood serum were tested.

The following animals were examined: *Heloderma*, turtle, pigeon, frog, guinea-pig, rabbit, dog. The results are as follows: on the whole the suspension of organs adsorbs less venom than does charcoal. The brains of the various species have relatively the

least adsorptive power of the organs examined; especially the brain of *Heloderma* has hardly any adsorbing power. On the other hand some other organs of *Heloderma*, namely, liver and kidney, have more adsorbing power than the organs of any other animal. Next in the order of adsorbing power come the organs of the turtle and these are followed by the liver and kidney of the pigeon, frog and guinea-pig, while dog and rabbit organs have least adsorbing power.

Certain differences seem to exist in the firmness with which the adsorbed venom is fixed to various organs. The kidney of *Heloderma* seems to hold the venom more firmly than the liver of the same animal. Of the greatest interest, however, appears to us the fact that the organs of *Heloderma* adsorb a larger quantity of their own venom than the organs of any other animal which we examined. While the blood of the *Heloderma* does not contain any antitoxin and, as Dr. E. P. Corson White has shown in our laboratory, no complement fixation takes place on mixing venom and blood serum of *Heloderma*, the liver and kidney of *Heloderma* show a definite specific relation to the venom of *Heloderma*, possessing a relatively great power of binding it. With some degree of justification it may be suggested that this specific relation is one of the factors concerned in the natural immunity of *Heloderma* against its own venom, such a union preventing the venom from a combination with certain parts of the nervous system. Furthermore, inasmuch as the adsorbing power of the brain is very slight, while on the other hand venom exerts its lethal action through its influence upon certain parts of the brain, we may assume that very small quantities of the venom when combined with brain substance are sufficient to kill the animal.

We wish to direct attention to the possibility that organs of those animals that are more closely related to *Heloderma*, as, for instance, the turtle, adsorbed more venom than more distinctly related animals, as the dog and rabbit. This, however, is merely brought forward as a suggestion and it must be left to further work to confirm or invalidate it.

58 (468)

A note on the parabiosis of rats and mice.[1]

By **R. A. LAMBERT.** (By invitation.)

[*From the Pathological Department of the College of Physicians and Surgeons.*]

This study includes 50 parabioses between rats and mice, twenty of which were terminated before the fifth day by the death of one of the animals, usually the mouse. That is, only thirty lived sufficiently long to admit of a union, or to determine if a union would take place. Of this number twelve showed a more or less complete tissue connection. One pair lived twenty-eight days, but the majority died between the seventh and fourteenth days. This compares favorably with the mortality observed where mice alone were used.

The technique employed consisted in a peritoneal anastomosis from 2 cm. to 3 cm. long, and a skin muscle apposition for about double this distance. Young rats weighing about forty grams were used, with "growing" mice from a large breed. Additional sutures through the skin of the shoulder and neck and adhesive plasters about the body gave sufficient fixation.

The existence of a true anatomical union is based on: (1) histological studies; (2) recovery in a second animal of substances injected into the first; (3) hemorrhage from one animal through the dead tissues of the other (noted twice).

The healing process is not essentially different from that taking place in the individual animal, except that in some instances the inflammatory reaction is more marked and the development into scar tissue slower. The skin unites with much less frequency than the deeper tissues — five cases out of twelve in this series. In many animals which fail to unite there is an absence of suppuration and the line of demarcation between the two tissues is indicated by an indefinite narrow zone of necrosis.

Seven parabioses between rats were made for comparative study. In one of these pair of three weeks duration, after death of one of the animals, incision was made in the dead rat nearly a centimeter from the line of union. A definite capillary oozing resulted. An injection of India ink was made immediately through

[1] This investigation has been done under the George Croker Special Research Fund.

the aorta of the surviving rat and the oozing blood was replaced by the injected fluid. These injections have been continued in the study of rat-mouse parabiosis, but in the injections so far attempted our technique has not been sufficiently satisfactory to make the results conclusive.

59 (469)

A demonstration of the inhibitory effect of magnesium upon normal and artificial peristalsis of the stomach and duodenum.

By **DON R. JOSEPH** and **S. J. MELTZER.**

[*From the Department of Physiology and Pharmacology of the Laboratories of the Rockefeller Institute for Medical Research.*]

Some years ago J. B. MacCallum[1] made the statement that purgation can be brought about by subcutaneous or intravenous injection of magnesium sulphate. He ascribed the effect to the stimulation of nerve and muscle tissue of the intestines by this salt, which thereby caused increased peristalsis.

In a paper by Meltzer and Auer[2] it was stated, however, that magnesium salts not only do not cause peristalsis, but directly inhibit it when normally present or even when aggravated by barium or physostigmin.

In opposition to this statement it was asserted in a paper by S. A. Matthews and D. E. Jackson[3] that after injection of magnesium sulphate the peristalsis shows no especial departure from the normal and barium and physostigmin show their usual action.

In order to obtain unbiased and incontestible evidence, the question was studied now by the graphic method. We employed for this purpose the following procedure. Rabbits only were used. A laparotomy was performed under anesthesia and a soft rubber catheter bearing a thin walled rubber ballon at its end, was introduced through an incision into the stomach and then pushed through the pylorus into a deep place in the duodenum. Another similar ballon was left in the stomach. All the incisions

[1] *Amer. Jour. of Physiol.*, 1903, x, 101.

[2] *Amer. Jour. of Physiol.*, 1906, xvii, 313.

[3] *Amer. Jour. of Physiol.*, 1907, xix, 5.

were then carefully closed. Next day and on the following days the catheters were connected with Marey tambours and the peristalsis studied graphically. The tracings show well defined characteristic waves produced by the contractions of the duodenum and stomach. These waves became greatly influenced — aggravated — by barium as well as by physostigmin. We shall not discuss here the character of these influences. We wish to point out only the effect of magnesium upon the peristaltic movements.

The tracings show in an unmistakable manner that the intravenous or intramuscular injection of a magnesium salt abolishes completely and for some time the normal peristalsis as well as the contractions of the duodenum and the stomach caused by barium and physostigmin. We shall not enter here upon any particulars. We wish, however, to add that our method differs from other methods employed for similar purposes in that (1) the intestines are not handled at all, and that (2) the peristalsis can be studied when the animal has completely recovered from the effects of the operation. We are utilizing this method for studying various phenomena pertaining to normal peristalis and shall report our observations in later communications.

60 (470)

Recovery from fatal doses of strychnin by the aid of curarin and artificial respiration (insufflation method).

By **A. O. SHAKLEE** and **S. J. MELTZER.**

[*From the Department of Physiology and Pharmacology of the Rockefeller Institute for Medical Research.*]

In a series of twenty-seven experiments upon dogs and cats we tried to develop a method by means of which life can be saved after fatal doses of strychnin. In all cases the strychnin was administered intravenously. In control experiments 0.4 mg. per kilo was invariably fatal, killing within an hour. By the aid of the method which will be described presently fourteen of the twenty-seven dogs used in developing the method survived the administration of fatal doses of strychnin. Of these fourteen five received 0.5 mg., three received 0.75 mg., and six received 0.8 mg. per kilo, that is, all animals received doses of strychnin which were in

excess of a fatal dose and which undoubtedly would have killed every one of these animals in less than an hour.

The method which we have employed consists (1) in instituting and keeping up artificial respiration by the continuous insufflation method; (2) in the intravenous administration of curarin from time to time in doses sufficient to control the convulsions; (3) in the injection of a small dose of atropin to meet the slowing of the circulation, and (4) in the infusion of a liberal quantity of Ringer's solution.

Against the fourteen survivors we had thirteen failures. An analysis of these failures, however, shows, first, that in most of these cases the insufflation was improperly adjusted or prematurely discontinued; second, that these animals received only a small quantity of Ringer's solution and in some instances no atropin. In other words, in the failures the method was not properly carried out. We, therefore, believe that we have good reasons for the hope that the above described method, when carried out properly, will prove successful in most cases of strychnin poisoning.

61 (471)

Intracellular proteolytic enzymes of liver.

By **A. R. DOCHEZ.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

The influence of reaction upon autolysis of animal tissues has been exhaustively studied. All observers agree upon the favorable influence of a weak acid medium, and upon the inhibitory effect alkaline reaction. As an example of the influence of reaction upon autolysis, 2.5 grams of liver after five days at 37 degrees yield the following equivalents of ammonia by the Kjeldahl method; in 0.4 per cent. acetic acid, 35.6 cubic centimeters N/10 H_2SO_4; in 0.2 per cent. acetic acid, 34.8 cubic centimeters N/10 H_2SO_4; in neutral, 11.3 cubic centimeters N/10 H_2SO_4; in 0.2 per cent. sodium carbonate, 4.8 cubic centimeters N/10 H_2SO_4; and in 0.4 per cent. sodium carbonate, 0.6 cubic centimeter N/10 H_2SO_4.

When normal liver is allowed to stand on ice for many days, the power to digest in alkaline medium increases markedly from

week to week until finally the enzyme solution is more active in alkaline than in acid medium. For instance, 2.5 grams of fresh liver after five days autolysis yields an equivalent in 0.2 per cent. acetic acid, of 29.4 cubic centimeters N/10 H_2SO_4; in neutral of 7.9 cubic centimeters N/10 H_2SO_4; and in 0.2 per cent. sodium carbonate, of 2.0 cubic centimeters N/10 H_2SO_4; whereas after standing fifty-five days on the ice the same liver gives in 0.2 per cent. acetic acid 17.6 cubic centimeters N/10 H_2SO_4; in neutral 21.7 cubic centimeters N/10 H_2SO_4, and in 0.2 per cent. sodium carbonate 24.2 cubic centimeters N/10 H_2SO_4. This rise of autolytic activity in neutral and alkaline media is analogous to the rise of tryptic activity of pancreatic extracts on standing, and is probably attributable to the slow conversion of an alkaline digesting enzyme from an inactive into an active form.

Activation of the alkaline enzyme can be accomplished more rapidly by pretreatment of fresh liver with weak acetic acid, a method first used by Hedin in demonstrating the alkaline enzyme of spleen. Two and a half grams of fresh untreated liver after five days autolysis at 37° C. yields an equivalent in 0.2 per cent. acetic acid, of 34.8 cubic centimeters N/10 H_2SO_4; in neutral, of 12.8 cubic centimeters N/10 H_2SO_4; and in 0.2 per cent. sodium carbonate, of 7.7 cubic centimeters N/10 H_2SO_4. The same liver, treated with 0.4 per cent. acetic acid for twenty-four hours on ice, gives after neutralization of the acid, equivalents in 0.2 per cent. acetic acid, of 22.5 cubic centimeters N/10 H_2SO_4; in neutral, of 17.2 cubic centimeters N/10 H_2SO_4; and in 0.2 per cent. sodium carbonate, of 16.8 cubic centimeters N/10 H_2SO_4. Previous treatment of fresh liver with alkali results in the destruction of practically all proteolytic activity. Two and a half grams of liver, treated for twenty-four hours on ice with 0.4 per cent. sodium hydrate, yield, after neutralization, an equivalent in 0.2 per cent. acetic acid, of 3.9 cubic centimeters N/10 H_2SO_4; in neutral, of 0.4 cubic centimeter N/10 H_2SO_4; and in 0.2 per cent. sodium carbonate, of 0.1 cubic centimeter N/10 H_2SO_4. There is some reason to believe that the inactivity following pretreatment of liver with 0.4 per cent. sodium hydrate does not represent destruction of the proteolytic enzymes, but is due to the fixing of the enzyme in the inactive state in which it exists in the cells. When fresh

pancreas is pretreated with sodium hydrate, the same type of inactivity results as is observed in like treatment of liver. This inactive pancreatic extract can readily be activated, however, by the addition of enterokinase. Furthermore, when liver, which has become active in alkaline medium by standing is treated with 0.4 per cent. sodium hydrate, inactivity which occurs when fresh liver is so treated is not produced.

In contrast to the effect of alkaline treatment upon the proteolytic enzymes of liver and pancreas is its effect upon the alkaline digesting enzyme of the polymorphonuclear leucocyte. It has been observed that the leucoprotease of the polymorphonuclear leucocyte maintains its activity when kept continuously in alkaline medium, and is able to effect proteolysis after treatment with sodium hydrate. From this observation it seems probable that leucoprotease exists in the cell in an active form.

The work outlined leads to the following conclusions. Autolysis of fresh normal liver progresses much more favorably in acid than in alkaline medium. Allowing liver to stand, and treating liver with weak acetic acid call into activity an enzyme which shows marked proteolysis in alkaline medium. This enzyme exists in the cell in an inactive form. Liver probably contains two proteolytic enzymes, one acting in acid and the other in alkaline medium. The inhibitory effect of alkali upon liver autolysis is referable to the preservation of the zymogen condition of the enzyme which acts in alkali. The maintenance of the equilibrium of the proteolytic enzymes of liver must be intimately dependent upon the preservation of tissue neutrality. The fact that leucoprotease is active after pretreatment with alkali suggests that this enzyme exists in the cell in an active form.

62 (472)

Enzymes and antienzymes of the blood serum with certain degenerative changes in the liver.

By **Eugene L. Opie** and **Bertha I. Barker.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

Since the liver undergoes advanced degenerative changes with chloroform poisoning it is possible that proteolytic enzymes are set

free and perhaps temporarily accumulate in the blood. Studies of Dr. Dochez (these *Proceedings*, p. 97) furnish evidence that the normal liver contains two enzymes : (*a*) The well known autolytic enzyme which causes proteolysis with greatest activity in a weakly acid medium, and (*b*) an enzyme which after activation with acid (like trypsin formed from trypsinogen of the pancreas) digests with greatest activity in a weakly alkaline medium.

The normal blood serum contains enzymes which digest proteins. Serum undergoes slight autolysis in the presence of an acid medium (0.2 per cent. acetic acid) but fails to autolyze in a neutral or alkaline medium (0.2 per cent. sodium carbonate). Nevertheless Hedin has shown that the globulin fraction of the serum obtained by one-third saturation with ammonium sulphate contains an enzyme which digests protein in alkaline or neutral media but is inactive in acid. The albumin fraction of the serum obtained by complete saturation with ammonium sulphate after removal of the globulin contains a thermo-labile antibody which inhibits the action of the enzyme associated with the globulin fraction, so that the mixture of globulin and albumin in the whole serum causes no proteolysis.

In our experiments the attempt has been made to determine if changes occur in the enzymes or antienzymes of the blood serum during the course of chloroform poisoning.

The following experiment, representing a considerable number, illustrates the increased proteolysis in acid which occurs at the end of three days as the result of daily administration of chloroform — at a time when there is advanced necrosis of the liver and temporary diminution or complete absence of the coagulability of the blood.

Autolysis of 3 c.c. of Blood Serum in Acid.

	First Day.	Fourth Day.	Fifth Day.
Control	1.0	1.1	1.8
After 5 days at 37° C.	3.7	5.05	4.9

No noteworthy increase of proteolytic activity in the presence of neutral or alkaline media is produced by poisoning with chloroform.

Since there is close analogy between degenerative changes in the liver and post-mortem autolysis, the attempt has been made to determine if with chloroform poisoning there is any loss of the

power of the serum to inhibit the autolysis of fresh liver tissue. The inhibiting action of serum of animals receiving chloroform when tested with normal liver or with liver of poisoned animals does not differ from that of serum obtained from normal animals.

It is noteworthy that fresh liver tissue autolyses with considerable activity in acid but is almost entirely inactive in alkali; liver treated for a time with acid acquires the ability to digest, like trypsin, in weak alkali. In order to test by a convenient method the ability of serum of animals receiving chloroform to inhibit an enzyme which digests in the presence of alkali the enzyme of polynuclear leucocytes was employed. A progressive increase of the anti-enzymotic action of blood serum has been found after administration of chloroform. The following experiment will represent many which have been performed.

The proteolysis caused by 20 mgr. of leucoprotease acting during five days at 37° C. is represented by 17.25 c.c. N/10 H_2SO_4. The figures obtained on different days with the same enzyme plus 0.5 c.c. of blood serum from an animal receiving chloroform daily are as follows:

1st Day.	*4th Day.*	*7th Day.*	*10th Day.*
13.75 c.c.	12.45 c.c.	5.25 c.c.	2.9 c.c.

Jochmann and Kantorowicz have shown that the anti-enzyme of blood serum is not specific for either trypsin or enzyme of leucocytes, for serum which exerts increased inhibition upon one has a parallel action upon the other. A series of comparative tests indicate that the serum which, as the result of chloroform poisoning exhibits increased power to inhibit the action of leucoprotease, exhibits a parallel increase of its power to inhibit the action of that enzyme of the liver which after treatment with acid digests in the presence of alkali.

The parallel between the enzymes and anti-enzymes which have been mentioned is indicated in the following scheme:

Enzymes in Liver.	Enzymes of Serum.	Anti-action of Serum.
1. Digesting in acid.	1. Digesting in acid. Increased by chloroform.	1. Alkaline reaction.
2. Digesting in alkali (Made active by treatment of fresh liver with acid)	2. Digesting in alkali (Contained in globulin fraction and inhibited by antibody of albumin).	2. Antienzyme inhibiting trypsin, leucoprotease and perhaps enzyme of liver. Increased by chloroform.

Chloroform which produces profound degenerative changes in

the liver increases in the blood serum an enzyme which like that of the fresh liver digests in acid; the alkalinity of the blood serum is capable of inhibiting this enzyme. A second enzyme capable of digesting in alkali is perhaps discharged by the degenerating liver; the blood serum acquires an increased ability to inhibit the action of similar enzymes. It is probable that increase of this antibody is the means by which the body protects itself from its own enzyme.

63 (473)

A preliminary note upon experimental lobar pneumonia with a demonstration of specimens.

By **R. V. LAMAR** and **S. J. MELTZER.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

Soon after the relationship of the pneumococcus to lobar pneumonia was established, a great many attempts were made to produce lobar pneumonia in animals. As early as 1888 Gamaléia claimed to have succeeded in producing pneumonia regularly in sheep and dogs by injecting pneumococci directly into the lung through the chest wall; but he failed when he made the injections into the trachea. From then until 1903 the attempts of all investigators have been successful in producing a pneumonia in only a relatively small number of experiments, and the inflammation has been usually of the lobular type. Wadsworth in 1903 was able to produce pneumonia with regularity by intratracheal injection only in immunized rabbits.

Dogs were used in our experiments. Under anesthesia a small stomach tube (as used in the intra-tracheal method of artificial respiration by Meltzer and Auer) is introduced through the larnyx into a bronchus and from 5 to 10 c.c. of a broth culture of a very virulent pneumococcus injected through the tube. The animals quickly recover without untoward results. Until now fifteen animals have been so treated. Of these four are under observation; nine have been killed at various periods of time after the injection — from one to six days; and two have died. All of the eleven animals which came to autopsy had pneumonia with consolidation of from one-half of one lobe to complete consolida-

tion of three lobes. The consolidation is quite similar in character to that occurring in lobar pneumonia of human beings. The lesion is a diffuse and evenly distributed (not patchy); exudative inflammation is attended by hemorrhage and the formation of fibrin. The pneumococci multiply in the affected part and they have been found to persist in those animals which were allowed to live longest (six days). In the nine animals which were killed the lesion was confined to the right lung. In the two which died there was involvement of both lungs. One died two days after the injection of a large amount of culture. Three lobes were completely consolidated and there was a generalized fibrino-purulent pleurisy and pericarditis and septicemia. The other animal, which had fever before the injection was made, died at the end of six hours. There was a generally distributed congestion and edema of both lungs, consolidation of one-half of the posterior right lobe and septicemia. None of the animals which were killed had septicemia.

Considering the regularity with which pneumonia has been thus produced it would seem that the method should afford valuable opportunity for studying pneumonia experimentally.

64 (474)

The effects of resection of one vagus upon serum anaphylaxis in guinea-pigs.

By JOHN AUER.

[*From the Department of Physiology and Pharmacology of the Rockefeller Institute.*]

In a previous communication by Lewis and myself[1] it was demonstrated among other things that the death of guinea-pigs in immediate anaphylaxis was due to the production of a stenosis in the pulmonary air passages so that air neither left nor entered the lung and we brought forward evidence which pointed to a tetanic contraction of the muscles of the bronchioles due to peripheral action as the immediate cause of this stenosis. This view has since been shared by Anderson and Schultz[2] and by Biedl and Kraus.[3]

[1] Auer and Lewis: *Jour. of the Amer. Med. Assoc.*, 1909, liii, 458. Auer and Lewis: *Jour. of Exper. Med.*, 1910, xii, 151.

[2] Anderson and Schultz: *Proc. of the Soc. for Exper. Biol. and Med.*, 1910, vii, 34.

[3] Biedl and Kraus: *Wiener klin. Woch.*, 1910, xxiii, 385.

On the basis of this conception, several series of experiments were carried out to determine, if possible, whether sensitization by the serum affected the vagus endings in the bronchial muscles, the muscles directly, or both structures. The experiments were carried out by sectioning one vagus in the neck, for according to Dixon and Brodie, the vagus of one side supplies the lung of that side only; moreover there is no evidence of a cell station between the pulmonary vagus fibers in the neck and bronchial muscle.

This report deals with only a part of the investigation. In one series of guinea-pigs, one vagus was resected in the neck thirteen days after the sensitizing dose of horse serum had been injected. The toxic dose was given intravenously from 30 to 57 days after vagus section. All of the nine pigs died with typical symptoms within five minutes after injection of the toxic dose. The lungs showed the characteristic picture of inspiratory immobilization on excision, and there was no characteristic difference between the innervated and non-innervated side.

In another series, one vagus was resected fifty-five days after the sensitizing dose, and the toxic dose was injected intravenously from 6 to 14 days after vagus section. These animals differed in no way from those of the other series.

In a final series one vagus was resected in normal animals. These experiments are not yet completed and will be reported later.

From the data given above it seems clear that the bronchial muscles themselves are sensitized by the horse serum in anaphylaxis.

65 (475)

Notes on the vaso-reaction in dogs produced by injections of extracts of the tubercle bacillus.

By **J. P. ATKINSON** and **CHARLES B. FITZPATRICK.**

[*From the Chemical and Research Laboratories of the Department of Health, City of New York.*]

This paper is a report of results in continuation of those read at the February meeting. Of especial interest are the results obtained with the blood serum of three tubercular calves which showed very slight lesions at autopsy. We obtained results

several months ago which led us to believe that dogs sensitized with tuberculin would show an arterial depression if injected upon the following day with tuberculin.

We have tested several "crude" tuberculins which have been heated in the autoclave at from 7 to 10 lbs. pressure for 30 minutes. The temperatures at these pressures varied approximately from 110° C. to 115° C. We have also tested the unconcentrated filtrate from he tubercular culture when it has reached a condition ready for concentration into "crude" tuberculin. Dogs sensitized with some of the samples of tuberculin which have been heated in the autoclave do not produce the reaction if injected upon the following day with the same tuberculin. Serum of dogs sensitized with the unconcentrated filtrate from the culture of *B. tuberculosis* of six weeks growth did produce a well marked reaction when injected into the dog on the following day.

A temperature of 105° C. was found to practically destroy the depressor substance in the unconcentrated filtrate.

The following are the experiments in detail as they were conducted:

Protocol of March 9.— Bull dog, 35 lbs., sensitized March 8, with 5 c.c. of a fresh preparation of crude tuberculin which had been heated in the autoclave for 30 minutes from 110° C. to 115° C.

1. 1 and 2 drops injected as usual, gave no results.

2. 2 drops of an older preparation of crude tuberculin used in January for sensitizing in experiments with tubercular serum gave a well marked depressor reaction.

3. 3 and 5 drops of the fresh tuberculin gave no reaction.

4. 6 drops of the January tuberculin gave a sharp reaction.

Protocol of March 11.— Dog, mongrel collie, 50 lbs., sensitized March 10, 1910, with 5 c.c. crude tuberculin which was heated in the autoclave for 30 minutes from 110° to 115° C.

1. 1, 3 and 10 drops of the tuberculin with which the dog was sensitized produced no reaction.

2. 10 drops of the same tuberculin after further concentration on the water bath produced a marked reaction.

3. 3 drops of the January tuberculin gave a slight reaction and 10 drops gave a sharp reaction.

4. 10 drops of the tuberculin used in the experiment of March 9 did not give a reaction.

Protocol of March 16.— Dog, 20 lbs., sensitized March 15, 1910, with 5 c.c. of an unconcentrated, unheated filtrate from the culture of B. tuberculosis ready for concentration.

1. 2 drops and 0.5 c.c. (10 drops) of this unconcentrated filtrate failed to give a reaction.

2. 3 c.c. of this unconcentrated filtrate gave a marked reaction.

3. 10 drops of the crude tuberculin used on March 11 gave a marked reaction, but 10 drops of crude tuberculin used on March 9 were inactive.

4. 1 drop of the tuberculin of January gave a very marked reaction.

5. 5 c.c. of this unconcentrated filtrate finally gave a marked reaction.

Protocol of March 18. — Dog, mongrel collie, 75 lbs., sensitized March 17, with 5 c.c. of the unconcentrated filtrate used March 16.

1. 10 drops of crude tuberculin used March 11 gave no reaction.

2. 5 c.c. unconcentrated tuberculin used to sensitize the dog failed to react.

3. 1½ drops of crude tuberculin of January gave a marked reaction.

Protocol of March 23. — Bull dog, 25 lbs., sensitized March 22, with 5 c.c. of the unconcentrated filtrate.

In this series of injections the unconcentrated filtrate was heated at different temperatures for one hour and water added afterwards to make the volume equal to the original volume.

The following temperatures were used:

35° C. original incubator temperature.
50° C. — 2 hours.
60° C. — 1 "
70° C. — 1 "
80° C. — 1 "
100° C. — 1 "
105° C. — 1 "

These heated preparations were made by Mr. Banzhaf; 5 c.c. were given at each injection. The injections were begun with the preparations which had been heated to 105° C. and given in order down to the original incubator filtrate. The 105° C. heated preparation gave only an indication of a reaction. The other preparations down to the original gave marked reactions.

The original unconcentrated filtrate gave a reaction which was not so marked as the heated preparations, but a later injection gave just as good a reaction. This dog which received these injections was used to test the sera of three calves which had been given intravenous injections of virulent cultures of B. tuberculosis, bovine.

These calves were killed and autopsied with results as follows: Calf No. 24. Strain 377. Injected Oct. 6, '09. Killed Mar. 22, '10. Small ¼ inch nodule with caseous center at site of injection.

Calf No. 17. Strain 96. Injected Aug. 12, '09. Killed Mar. 22, '10. ¼ inch, tubercle in prepectoral node.

Calf, No. 25. Strain 558. Injected June 10, '09. Killed Mar. 22, '10. Fibrous area at site of injection, small amount of caseous material. Calcification.

These calves gave practically no physical signs of tuberculosis. The injection of 4 c.c. of serum of each of these calves produced the characteristic reaction which we have described. Serum drawn from a normal calf did not give a reaction. This calf was kept in the same stable and under the same conditions as the three injected calves.

Protocol of March 25. — Bull dog, 35 lbs., sensitized with 10 c.c. of the unconcentrated filtrate. Primarily used to test a normal calf kept with and under the same conditions as the three previous calves.

1. 3 and 4 c.c. respectively of this normal calf serum failed to give a reaction.

2. Injections of 4 c.c. from each of the tubercular calves failed to react.

3. 5 c.c. of unconcentrated filtrate, which had been heated to 60° C. and tested on March 23, gave a marked reaction.

CONCLUSIONS.

1. Dogs injected with 5 c.c. of tuberculin or of the unconcentrated filtrate become sensitized to tuberculin, and an injection of tuberlin (1 drop in some cases) given the following day produces a drop in arterial pressure.

2. The depressor substance is not affected by heat up to and including 100° C. during a period of one hour.

3. If the tuberculin is kept at 105° C. for one hour the depressor may be lost or greatly diminished.

4. The results of the serum of tubercular calves injected into the sensitized dog seem to indicate that the method outlined in our previous paper can be used for the early diagnosis of tuberculosis.

5. This depressor substance seems to be different from the depressor substance of tuberculin in that the tuberculin depressor substance is much more stable; while the depressor substance of tubercular serum may be lost when the serum is kept in the ice box.

6. These experiments possibly give us a method for standardizing tuberculin by noting the minimal quantity which will cause a reaction in blood pressure.

66 (476)

Immunity to the growth of cancer induced in rats by treatment with mouse tissue.[1]

By ISAAC LEVIN.

[*From the Department of Pathology of Columbia University, at the College of Physicians and Surgeons.*]

The opinion prevails among investigators that resistance to growth of tumor can be induced only by treatment with tumor or normal tissue of the same animal species. In the course of a study on different phases of atreptic immunity, a series of experiments was undertaken with the aim in view to find the means whereby mouse tumor may be made to grow on a rat and *vice versa*. Ehrlich, in his so-called zig-zag transplantations, has shown that such a tumor of a mouse inoculated into a rat grows normally for eight or ten days and then ceases its growth and be-

[1] This research is conducted at the expense of the George Crocker Special Research Fund.

comes absorbed. Our experiments consisted in the subcutaneous inoculation into a rat, of the normal skin and spleen tissue of a mouse followed in a few days by a subcutaneous inoculation of Ehrlich's sarcoma of a rat. The aim of this treatment was to accustom the tumor cells to mouse tissue, and then to see whether such a rat tumor, which may have obtained during its growth the food supplied by the inoculated normal mouse tissue, would not grow more readily when inoculated subsequently into a mouse. The results of this investigation were negative, but the extremely interesting fact was observed that a certain number of the rats treated with mouse tissue appeared immune against growth of the rat sarcoma. The following table will illustrate this phenomenon :

	Treated Animals.	Controls.
No. of rats inoculated with tumor.	40	40
No. of rats survived at the final examination.	27	40
No. of rats with tumors.	10	36
Per cent. of takes.	37 %	90 %

Similar positive results were obtained recently by C. Lewin, who succeeded in immunizing rats with mouse tumor and *vice versa*.

It would seem that this discovery of the possibility of immunizing an animal against growth of tumor by treatment with alien tissue not only adds a new fact to the study of artificial immunity, but is also of some theoretical interest. It would appear that Ehrlich's atreptic theory, with which he explains all the phases of tumor growth, while possibly of great importance in the explanation of certain facts, probably does not have a universal application. According to this theory the tumor of a rat grows within that animal because it finds there the necessary specialized food. On the other hand, organ cells of a mouse do not possess, nor do they require the specific food of the rat and this is the reason why a rat tumor fails to grow indefinitely in a mouse. When a rat is immunized against growth of rat tumor by previous treatment with mouse tissue, such a failure to grow cannot be ascribed to the lack of proper nourishment within the host, since the previously inoculated mouse cells could not assimilate such food. The explanation must rather be sought in some protective substances within the host created under the influence of the implanted mouse tissue.

67 (477)

The early stages of the spontaneous arterial lesions in the rabbit.

By **ISAAC LEVIN** and **JOHN H. LARKIN.**

[*From the Department of Pathology of Columbia University, at the College of Physicians and Surgeons.*]

Since the first publication of Josué in 1903, who succeeded in producing artificial arterio-sclerosis by intravenous injection of adrenalin, a great deal of work has been done on the subject. Successful results were reported by treating animals with digalen, barium chloride, hydrastin, nicotine and a number of other substances. The lesions thus produced resemble closely the atheromatous degeneration in the human aorta.

The site of the lesion is usually the ascending portion or the arch of the aorta. The process occurs primarily in the media of the vessel wall and consists in necrosis of the smooth muscle cells, thickening and breaking up of the elastic fibers, and the appearance of calcareous deposits in the diseased areas.

All these successful experiments with the production of artificial arterio-sclerosis were obtained only in rabbits. All efforts to produce similar results in other laboratory animals failed. The question consequently suggested itself whether the success with the rabbit is not due to the frequency of the spontaneous occurrence of this disease in the animal. Indeed several reports were made on the spontaneous occurrence of arterio-sclerosis in the rabbit. A. B. Miles makes a most remarkable statement in this respect. In 61 rabbits treated with adrenalin he found arterial lesions in 17 animals, which represents 27.86 per cent., while of 49 normal rabbits he found the same condition also in 17 animals, which represents 34.77 per cent. R. M. Pearce found spontaneous arterial lesions in 6 per cent. of animals. M. C. Hill found the lesions in 15 per cent. of 210 animals examined.

All these investigations show that while spontaneous lesions are met with in rabbits the percentage of the diseased vessels is far lower than the percentage of the lesions found after treatment with adrenalin and the other substances. But since all the investigations arrived at their conclusions only by gross inspection, the

question very naturally presents itself whether spontaneous lesions could not be found more frequently if every vessel which appears normal were examined microscopically. It seems plausible *a priori* to suppose that before a lesion develops to such a degree that it may be noticed on gross inspection, the beginning of it may be so minute as to be discovered only by microscopical examination.

With this aim in view, 240 rabbits were examined. All these animals were used for laboratory purposes, mainly for obtaining blood-serum, and no toxic substance of any kind was introduced into these animals. On gross inspection of the aorta of these 240 rabbits, 31, or 13 per cent., had gross lesions and these were not examined any further. Of the remaining 209 animals, every arch of the aorta (the part of the aorta which is most frequently affected with spontaneous and arterial lesions) was examined microscopically. The specimens were hardened in formalin, imbedded in celloidin or paraffin, and stained with hematoxylin-eosin and Weigert's elastic tissue stain. Of the 209 vessels examined, 78, or 37.3 per cent., presented minute lesions visible under the microscope. The lesions showed either the degeneration of the media including the muscular and fibrous tissue coat with the elastic fibers preserved, but thickened and tortuous, or the same degeneration of the media with loss of muscular and elastic fibers and deposition of calcium. In other vessels, again, the main condition was proliferation of the endothelial cells of the intima.

Thus in our investigation we found in 52 per cent. of the examined rabbits arterial lesions of different degrees or development. This percentage corresponds very closely to the percentage of the diseased vessels found after adrenalin or other treatment.

While the results of this research cannot prove with absolute certainty that in some cases arterial lesions may not be produced solely by the injections, the possibility seems to be great that the treatment frequently only enhances or ripens an early stage of arterial disease that existed in the vessel before treatment. It would seem, therefore, that the rabbit is not a suitable animal for the study of experimental arterio-sclerosis.

68 (478)

Artificial cyclopia in the smelt.

By **J. F. McCLENDON.**

I found that about about 0.1 per cent. of the smelt embryos in the fish hatchery at Cold Spring Harbor, L. I., had abnormal eyes. There were all degrees of approximation and "fusion" of the two eyes, sometimes resulting in perfect cyclopia. Less often one eye was imperfectly developed or absent (monophthalmia asymmetrica).

Preliminary experiments show that the percentage of abnormal eyes was increased by the addition of anaesthetics or magnesium chloride to the water, or by inhibiting the gaseous exchange.

It was thought improbable that much of the magnesium entered the embryos. If sub-lethal percentages of neutral salts are added to the water in which adult fish live, very little salt enters their bodies. As the lethal dose is approached, asphyxiation commences and salt enters the fish in larger amounts.

It was not practicable with the material at hand to make accurate chemical analyses of the embryos, but microchemical tests showed no more chlorides in the embryos developed in M/5 $MgCl_2$ than in those developed in tap water. One demonstration that salts enter fish embryos is that in pure potassium chloride solutions the heart stops beating. No increased amount of potassium was found by microchemical tests, in embryos kept in M/5 KCl until the heart stopped beating, than in the controls.

If the magnesium does not enter the embryos it must act on the surface, and since its effect is similar to that of deficient aeration, I suggest that the magnesium alters the surface so as to retard the entrance of oxygen or the exit of carbon dioxide. Anesthetics that are known to penetrate freely may nevertheless produce their charactistic effect by altering the surface.

69 (479)

Cataphoresis of proteids in the living cell.

By **J. F. McCLENDON.**

In cells of the newt, the frog, the onion and the hyacinth, on the passage of an electric current, the basic-staining proteids move toward the anode and the acid-staining toward the cathode.

These substances do not pass through the cell or nuclear membranes, but the nuclear membrane is often pushed out toward the anode by the pressure of the (basic-staining) chromatin.

During the process of mitosis, however, the above rules do not hold. As the process of mitosis advances, more current is required to move the chromatin, and more acid-staining proteid is carried along with it. After the mitotic spindle is formed, it (including the chromosomes) is carried toward the anode without alternation of its axial orientation.

These facts disprove the hypothesis that the chromosomes are drawn to the poles of the spindle by electrostatic stress, the poles and chromosomes being of opposite sign, for if this were true, the poles of the spindle would not move toward the anode with the chromosomes, but would move toward the cathode.

It is probable that the mitotic spindle consists chiefly of proteids in the "gel" phase, and that this gelation prevents the separation of acidophile and basophile substances by the current. That the cells were not killed and the spindles coagulated, during the experiments, is demonstrated by the fact that a cell in which the spindle was displaced by the current divided. In this case the cytoplasm was divided unequally, as the division passed through the equator of the displaced spindle.

70 (480)

Nitrogen and sulphur metabolism in morbus ceruleus.

By **N. B. FOSTER.**

In morbus ceruleus due to congenital cardiac defect there are found two conditions which suggest that in this disease the tissues are not so adequately furnished with oxygen as in health. These conditions are the abnormally high carbon dioxide content of the venous blood (Lepine) and the erythrocytosis, the latter being a direct response of the hemopoietic tissues to a lowered oxygen tension (Seller). It would seem plausible that in some severe cases the metabolism might be altered by the conditions mentioned. The case observed in this study was a child that presented all the features of morbus ceruleus due to congenital cardiac defect. Analyses of the urine failed to show anything abnormal in the nitrogen partition. The comparison of the amounts of

neutral sulphur, wherein deficient oxidation would be most apt to be manifested, with the amounts of a normal child, shows very slightly higher figures but the difference is not sufficient to justify the conclusion of deficient oxidation.

71 (481)

On parenteral protein assimilation.

By **P. A. LEVENE** and **G. M. MEYER.**

[*From the Department of Chemistry of the Laboratories of the Rockefeller Institute for Medical Research.*]

The results of recent work on the fate of protein introduced parenterally led to the conviction that such protein is assimilated and utilized by the organism in the same manner and in accordance with the same laws as protein ingested *per os*. However, there exists a considerable divergence in the views on the mechanism by which this assimilation is accomplished.

Very recently Freund advanced a theory that protein introduced into the organism subcutaneously or through the circulation is eliminated into the intestinal tract where it undergoes the usual digestion and absorption.

The present investigation aimed to test the correctness of the last theory. An animal deprived of its jejunum and ileum was placed on a standard diet and brought into a condition of nitrogenous equilibrium. On the days of experiments the animal received a subcutaneous injection of horse serum, heated for one half hour at 60° C. The volume of injected serum was equivalent to 1.5 grams of nitrogen. The elimination of additional nitrogen was followed for several days following the days of the serum injection. In all experiments was noted a complete retention of the protein introduced parenterally in the same manner as this occurs in normal animals. Thus the theory of Freund is contradicted by the results of our experiments.

72 (482)

A method of isolating the cerebro-medullary circulation.

By **ARTHUR BRADLEY EISENBREY.**

[*From the Carnegie Laboratory of New York University.*]

In a recent study by Dr. R. M. Pearce and myself of the mechanism of certain experimental conditions of low blood pressure, the following difficulties were encountered:

1. When substances that have been shown by special experiments to exert a selective peripheral action are injected into the circulation of an intact animal, the results frequently point to some additional central action that tends to mask or to neutralize to some extent the usual peripheral action.

2. Substances that have an essentially central action may sometimes produce results to be explained only on the basis of an added peripheral influence.

3. In experiments accompanied by a condition of extreme low blood pressure it is often difficult to know whether to ascribe these final results directly to the primary assault on the central or peripheral mechanism respectively, or to the additional secondary effects produced by the cerebral anemia that is the concomitant of the lowered systemic blood pressure. It is evident, therefore, that a knowledge of the extent and importance of the part played primarily by the central and peripheral mechanisms respectively, and by the central mechanism secondarily, in the production of any given result, is necessary for the interpretation of the mode of action of the substance used.

The chief difficulty is the impossibility in an intact animal of limiting a substance to the cerebro-medullary, as contrasted with the spinal and peripheral portion of the vasomotor system, or *vice versa*. It was apparent that this difficulty could be overcome only by isolating the circulation of the head and neck from that of the trunk and then transfusing the blood from another dog. If this could be accomplished it would be possible to obtain relatively pure central and peripheral results by the injection of solutions into either of the two independent circulations. The following procedure has been worked out on the dog.

Under full ether anesthesia, the right common carotid artery of the animal to be experimented upon, called hereafter the recipient, is freed for its entire length and a ligature is placed loosely about it. When it is desired to have none of the injected solution reach the donor's circulation, and in short experiments, the external jugular vein on the left side is similarly freed and is later used for the outlet of the venous blood. The femoral artery is prepared for taking manometric records and likewise the saphenous vein of the opposite side for the injection of solutions into the circulation of the trunk.

When the experimenter is ready to institute artificial respiration, the thorax is opened by sawing through the entire length of the sternum. This gives rise to very little hemorrhage and, if the sterno-cleido-mastoid muscles are detached from their origin, allows free access to the vessels at the base of the heart. The two pairs of sternal vessels are now double ligated and cut between the ligatures. A full exposure of the superior vena cava is thus provided. By carefully separating the loose tissue over it the nerves which run alongside may be avoided and a ligature passed around the vessel just above the entrance of the azygos vein. The large brachio-cephalic artery which lies just behind and to the left of the vena cava is exposed by blunt dissection at its point of origin from the arch of the aorta, and a ligature passed about it. The second large arterial branch, the left subclavian, best approached through the left side of the mediastinum, is similarly treated. Ligation of the subclavian arteries requires the greatest care, for it is essential to have the ligatures so placed as to occlude the thyroid axis, superior intercostal and suprascapular arteries, which might, through their anastomosing branches, form a communication with the circulation of the trunk. The same care in the ligation of the corresponding *veins* insures against the passage of venous blood from the trunk into the cerebral circuit.

The right common carotid artery which has already been freed is ligated and severed at its upper end, and, by the method of vessel anastomosis described by Crile, its central end is attached to the central end of a carotid artery of the donor, preferably a larger dog, and the isolation of the cerebral circulation of the recipient is next performed.

By means of the ligatures that have been placed about them the large vessels are raised and clamped. First the left subclavian and then the branchio-cephalic arteries are clamped close to the aorta. Simultaneously the blood is allowed to pass through the transfusion anastomosis. The exposed left external jugular vein is then opened close to the subclavian branch to allow venous outflow from both directions and the superior vena cava is raised and clamped. When it is desired to have a complete circulation between the donor and the cerebral circulation of the recipient, a second anastomosis is made between the central end of the right

external jugular veins of the recipient and the central end of a similar vein in the donor, omitting the opening of the vein in the left side of the recipient's neck. This prevents the early termination of the experiment by the exsanguination of the donor.[1]

By this procedure, the arterial supply of the recipient's head and neck is maintained through the right vertebral and left common carotid arteries, both of which are branches of the brachiocephalic artery. The venous outflow is maintained by the unobstructed passage of the blood into the superior vena cava from which it escapes through the external jugular vein on the right or left side as the case may be.

Injections may be made into the cerebral circulation of the recipient through a hypodermic needle inserted in the carotid artery in the region of anastomososis, or through a canula placed in the central end (clamped) of the superior thyroid artery. It is also evident that the solution may be given intravenously in the donor, but under such circumstances the influence of changes in the arterial blood pressure of the donor must be considered.

By this method of isolation, physiological experimentation upon altered cerebral blood pressure is rendered feasible by (1) diminishing the venous outflow through the jugular anastomosis, (2) by constriction of the arterial anastomosis, or (3) by raising the donor's general blood pressure.

The success of this method of isolation is evidenced by the fact that an injection of horse serum into the cerebral circulation of a sensitized animal does not cause the typical fall of blood pressure which is characteristic of anaphylactic shock, while a subsequent injection into the trunk does cause such a fall.

73 (483)

A reversion of the starch-dextrin reaction.

By EDWARD TYSON REICHERT.

[*From the S. Weir Mitchell Laboratory of Physiology, University of Pennsylvania.*]

In the reversions of enzymic and catalytic processes heretofore recorded, the synthesis has been brought about by a high concen-

[1] Before making the venous anastomosis it is essential to ascertain whether there is an efficient back flow from the superior vena cava through the central end of the recipient's right external jugular vein. To provide this it is frequently necessary to rupture the valves that are present just above the subclavian branch.

tration of the products of analysis, or by the addition of *fresh* enzyme to a solution that had reached a state of equilibrium. In the starch dextrin reversion the synthesis was attempted in an entirely different and original way, that is, by a rapid increase of temperature of a solution that is near or at the point of equilibrium in relation to substances studied. In accordance with a known law this change of temperature should move the point of equilibrium *endothermically*.

In studying this phenomenon it must be borne in mind that in the digestion of liquid boiled starch there may be going on coincidently at least three independently but serially related processes which are dependent upon the activities of three enzymes — one, in the depolymerization of the liquid starch into dextrins (*amylase*); another, in the hydrolysis of dextrins into maltose (*dextrinase*); and another, in the hydrolysis of maltose into glucose (*glucase*). Each of these enzymes has its own optimal point of activity; each carries on its own reaction independently of the others; and in each reaction the substances entering into the reaction have their own point of equilibrium of solution independently of the other reactions. Hence it follows that each reaction, in so far as concerns the reversion phenomenon in relation to the enzyme and the concentration of the solution and the temperature, must be studied separately. Conditions may be present that are favorable to the reversion of one of the reactions but not of the others.

In most of these experiments there was used 50 c.c. of a one per cent. solution of boiled starch with 25 c.c. of a three per cent. solution of Merck's "pure pancreatin." In a few experiments ptyalin, malt diastase or Taka-diastase was substituted for pancreatin, and in some modifications were made in the concentration of the enzyme. Digestion was usually carried on at room temperature, but sometimes at 37° C. The chief procedures and results may be summarized as follows:

1. If at any time after the reaction has proceeded so far that the addition of a two per cent. Lugol's solution yields a *violet* reaction (even though there be but the merest trace of coloration) the preparation be heated quickly to the optimal point of saccharification (approximately 60° to 65°) the composition of the solution is so altered that the addition of iodine now yields a *blue* reaction,

which is accepted as being characteristic of starch. (Claude Bernard found a form of glycogen in paralyzed muscles which gave a blue reaction with iodine.) The blue coloration is proportional to but more intense than the corresponding violet previously obtained, so that even when the violet coloration was scarcely discernible a good blue reaction was observed. The optimal temperature of the starch-dextrin reaction is distinctly higher than the temperature at which the reversion occurs, but the exact point has not been determined. The occurrence of the reversion at the optimal temperature of saccharification is doubtless merely a coincidence.

2. When digestion has proceeded to the point at which there is not a color reaction with iodine, in other words to the achroödextrin-sugar stage, heating the preparation as above did not cause either a starch-dextrin or an erythrodextrin-achroödextrin reversion, as was shown by the continued absence of any color reaction with iodine.

3. By testing the preparations before and after heating with the usual copper-reducing tests, and with the polariscope, both dextrin-maltose and maltose-glucose reversions were occasionally detected, but the results were very inconstant and generally not absolutely conclusive. The absence of a constant occurrence of these reversions is doubtless owing to a failure to obtain the exact concentration of solution in relation to temperature.

4. The starch-dextrin reversion is not permanent unless the preparation has been heated to the temperature at which the enzyme is destroyed. Upon cooling a preparation that has been heated to only a lower level a reconversion of the starch into dextrin occurs, with of course a loss of the blue reaction and a return of the violet reaction with iodine.

5. The starch-dextrin reversion is not enzymic, but dynamic, and, therefore, the mechanism is quite different from that of the reversions recorded by previous observers. Formaldehyde in even small amounts is, as is well known, highly destructive to amylase, and when added to the starch-dextrin solution absolutely prevents the reversion. This might be taken as showing that the absence of reversion is due to the destruction of the enzyme, but this is negatived by the fact that the addition of strong mineral acids in

quantities sufficient to instantly destroy the enzyme does not prevent reversion. Unusual interest is attached to the starch-dextrin reversion, not only because of the phenomenon *per se*, but also because it is not enzymic, and because formaldehyde prevents it. How formaldehyde is effective is problematical.

74 (484)

The rôle of alkali in the development of the sea-urchin.

By **JACQUES LOEB.**

In a former paper (1898) I have shown that the velocity of development of the eggs, is within certain limits, a function of the concentration of the hydroxylions in the surrounding solution; and I pointed out the probable connection of the action of bases with oxidations. In a later paper (1906) it was shown that at a concentration of hydroxylions below, but very close to, the point where neutral red indicates an alkaline reaction (*i. e.*, near the point of neutrality) the eggs cannot develop beyond the eight cell stage.

If we put fertilized and unfertilized eggs of Purpuratus into seawater to which a drop of neutral red has been added, at first, the fertilized and unfertilized eggs take the stain equally well. If we later transfer the eggs into seawater which is free from neutral red, the fertilized eggs gradually take all the stain while the unfertilized eggs become in the same measure decolorized. The explanation for this phenomenon lies in the fact that in the fertilized egg the neutral red enters into a chemical combination by which it becomes undiffusable; while in the unfertilized egg the neutral red is only held in solution. Since neutral red is a base it is to be presumed that the body in the egg with which it combines is an acid.

This suggested the possibility that the above mentioned acceleration of the development of the egg by other bases, *e. g.*, sodium or potassium hydroxide, might be due to a combination of these bases with the same acid with which neutral red combines in the fertilized egg. If this assumption were correct it should be expected that the addition of two or three drops of a 1/100 gram-molecular solution of neutral red to a neutral van't Hoff solution (in which the fertilized eggs cannot develop) should cause the eggs to develop into swimming larvæ. The experiment was tried and it was found that neutral red has indeed such an effect.

This observation shows that alkali allows or accelerates the development of the egg through the neutralization of an acid. It is possible that we are dealing here with one of the cases which conform with Stieglitz's theory of catalysis by salt formation.

75 (485)

How can the process underlying membrane formation cause the development of the egg?

By **JACQUES LOEB.**

In a series of previous papers it was shown that the process underlying the formation of the fertilization membrane is the essential act in the causation of development. It was further shown that this process is essentially a cytolysis or liquefaction of the superficial (cortical) layer of the cytoplasm of the egg. The question arose, how can this cytolysis or liquefaction cause the egg to develop. It seemed natural to think first of the possibility that the superficial cytolysis rendered the egg more permeable for substances required for its development.

The possibility that fertilization might increase the permeability of the egg had been considered by me in 1906 (*Biochem. Zeit.*, 1906, ii, 87). I had found that a pure solution of sodium chloride is practically harmless for the unfertilized, but very toxic for the fertilized egg. Since lack of oxygen is likewise harmless for the unfertilized and very harmful for the fertilized egg, I was inclined to ascribe the difference in the toxic effect of sodium chloride to a difference in the velocity of chemical reactions and not to a difference in the permeability of the fertilized and unfertilized egg. I have recently resumed the investigation of this question with regard to the action of salts, alkalis and acids.

(*a*) *The action of salts.* — As stated, a pure solution of sodium chloride kills the fertilized egg much more rapidly than the unfer tilized egg. In the preceding notice we have stated the concentration of hyroxylions below which the egg of Purpuratus can no longer develop. I find that below this limit a pure sodium chloride solution is much less toxic for the fertilized egg than above that limit. These experiments confirm the view that the difference in the toxic effects of a pure sodium chloride solution on the fertilized and unfertilized egg is due to a difference in the

velocity of chemical reactions and not to a difference in permeability.

(*b*) *The action of alkali.*— Sodium hydroxide injures or destroys the fertilized egg much more rapidly than the unfertilized egg. The experiments with neutral red mentioned in the previous paper indicate that this base diffuses equally well into the fertilized and the unfertilized egg but that in the former it enters into chemical combination, while in the latter it remains in solution. It can be shown that the toxic action of a comparatively high concentration of sodium hyroxide (e. g. N/500) upon the unfertilized egg can be enormously reduced through the addition of a trace of potassium cyanide, while in the fertilized egg the protective effect of potassium cyanide or lack of oxygen is equally noticeable, but for weaker concentrations of sodium hydroxide.

(*c*) *The action of acids.* — It was found that unfertilized eggs are killed by acids as rapidly as fertilized eggs.

All my attempts to show that the process of membrane formation causes the development of the egg by increasing its permeability have thus far met with negative results.

It is, however, possible to account in another way for the fact that the cytolysis of the cortical layer of the cytoplasm starts the development of the egg. In the process of cytolysis certain substances which were solid are liquefied and enabled to diffuse into the egg. If it could be shown that these substances were of such a nature as to start or accelerate the chemical processes underlying development the connection between membrane formation and causation of development would become intelligible.

76 (486)

A study of the origin of the immune bodies by the method of organ transplantation.

By **ARNO B. LUCKHARDT.** (By invitation.)

[*From the Hull Physiological Laboratory of the University of Chicago.*]

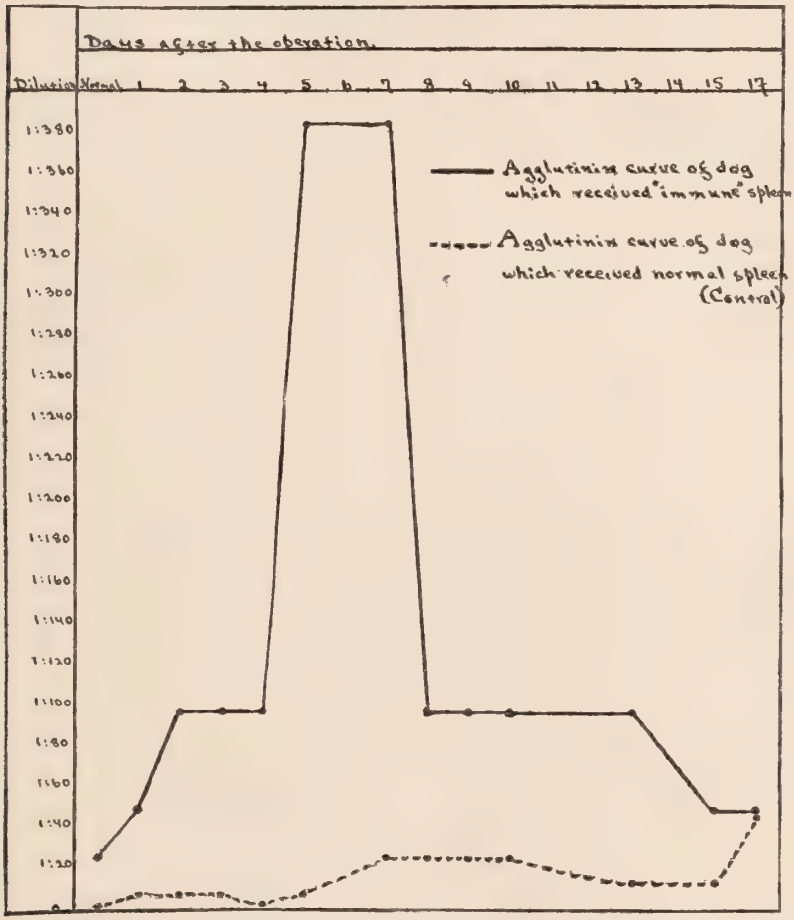
The interesting facts recently published by Prof. Hektoen and Prof. Carlson on antibodies and their formation indicate strongly that the blood takes no direct part in the fixation of antigen (goat's and rat's corpuscles) or in the production of antibodies (lysins and agglutinins) for these corpuscles. What tissue or tissues, if not the blood, fix the antigens as early as three hours after intravenous injection?

The organs which fix the antigens are undoubtedly also the organs intimately concerned with the production of the specific immune bodies for these antigens. Previous work on the origin of the antibodies, in general, strongly suggests that the hemopoietic organs (spleen, lymph glands, and bone marrow) are the source of the immune bodies. If, therefore, the antigens are fixed in part by the spleen, successful transplantation of that organ from one dog immunized 24 hours previously with goat's blood into a normal dog ought to cause the appearance of the specific lysins and agglutinins in the blood and body fluids of the latter. The technical difficulties involved in the transplantation of the spleen are great and so far the operation has not been performed by me as successfully as has recently been reported by Dr. Carrel.

In the meantime the following indirect method of attacking the problem was chosen. The spleen of a dog immunized 24 hours previously by an intravenous injection of goat's corpuscles is removed aseptically and ground up by means of a sterile meat grinder. The mass is suspended in warm physiological salt solution and introduced into the peritoneal cavity of a normal dog. The dog is bled at regular intervals for about three weeks. The sera kept in the ice chest are tested under the same conditions and on the same suspension of goat corpuscles at the end of that period.

The following considerations form the basis for this procedure. If the splenic tissue fixes the antigen either, or both, of two things

may happen when the macerated "immune" spleen is introduced into the peritoneal cavity of a normal dog. The splenic cells may escape death and give rise to the antibodies in the second dog; or the antigen may be split off again on the death of splenic cells (on Ehrlich's conception of antigen fixation) and reaching the cir-



culation may again attach itself to suitable receptor and thus stimulate to specific antibody production.

With this method the spleen has given results so striking that I shall include the specific agglutinin curve of a single experiment on a dog which had received intraperitoneally emulsified spleen of another dog immunized 24 hours previously with an intravenous

injection of 1 c.c. of a 10 per cent. suspension of washed goat's corpuscles per kilo body weight. The control animal received intraperitoneally an emulsion of spleen from a normal dog (see curve).

Never does the serum of the control dog cause agglutination in greater dilution than 1:48. The agglutinating power is, on the whole, less than 1:24. The serum of the dog which received the immunized dog's spleen showed an increase in agglutinin from the start. Rising from a normal of 1:24 the serum agglutinates on the fifth and seventh day in a dilution of 1:384. From the eighth to the thirteenth day the serum agglutinates in a dilution of 1:96; and on the seventeenth day, the day of testing the fluids, the serum possesses an agglutinating value of only 1:48.

A future paper will give in greater detail this and other experiments which have yielded similar results with respect to antigen-fixation by the spleen. The mechanism of subsequent antibody formation in the recipient, whether by growth of the living cells or a second fixation of antigen liberated by the dead or dying splenic cells remains an open question. The results so far obtained warrant the conclusion that the spleen fixes antigen; and that this organ is, therefore, necessarily concerned with antibody formation.

The same method has been used with lymph glands and bone marrow with negative results. The work is being continued along this line with the hope of proving the point directly and conclusively by the successful transplantation of the spleen.

77 (487)

The concentration of ammonia in the blood of dogs and cats necessary to produce ammonia tetany.

By **CLARA JACOBSON**. (By invitation.)

[*From the Hull Physiological Laboratory of the University of Chicago.*]

The importance of this subject rests in its relation to the markedly increased ammonia content of the blood of animals in parathyroid tetany. In a recent paper,[1] evidence was presented which indicates that this increased ammonia is apparently asso-

[1] Carlson and Jacobson: *American Jour. of Physiol.*, 1910, xxv, 403.

ciated with an impaired liver activity. That there is a marked similarity of the symptoms of ammonia poisoning and meat intoxication after Eck fistula to those of complete thyroidectomy was also pointed out and is further confirmed by the present work. These experiments were carried out at the suggestion of Dr. Carlson with the view of determining whether the ammonia concentration in the blood of animals in parathyroid tetany is sufficient by itself to cause tetany, assuming that no tolerance to the ammonia is developed.

Slow injections of ammonium carbonate in solution were made intravenously, the saphenous vein in dogs, and the jugular vein in cats being used. Blood samples were drawn for analysis when the symptoms became of the severity usually observed in parathyroid tetany or had returned to such after excessive injection. Some differences in ammonia content are inevitable and are due to the rapid diffusion of the ammonia into the tissues and the lymph, to elimination by the kidneys and to conversion into urea by the liver. The results obtained are as follows:

Ammonia Content of the Blood in Mgr. per 100 c.c.

Dog No. 1	2.8	Cat No. 1	3.44
" No. 2	2.1	" No. 2	3.64
" No. 3	3.7	" No. 3	1.88
" No. 4	1.75	" No. 4	2.40
" No. 5	2.4	" No. 5	2.34
		" No. 6	2.47
		" No. 7	3.18

Blood samples of six normal and three thyroidectomized dogs in tetany were analyzed for comparison and found to average: normal, 1.438, thyroidectomized 2.73 mgr. per 100 c.c. The ratio for cats is: normal (average for five animals), 1.57, and thyroidectomized (average for six animals), 2.53.

The symptoms observed after ammonia injection are very similar to those of complete thyroidectomy. There is a preliminary phase of dyspnœa and salivation usually accompanied by depression and more or less somnolence. Further injection results in twitching of muscles, which may be suddenly followed by opisthotonus and respiratory standstill (a condition observed in three or four parathyroidectomized cats under observation last fall).

In recovery, tremors, tetanic spasms, or both, and marked hyperexcitability are noted.

The results support the view that the increased ammonia in the blood of parathyroidectomized animals is directly responsible for the tetany and depression symptoms, as the concentration of the ammonia in the blood of parathyroidectomized cats and dogs is sufficient to cause tetany, tremors and depression in the normal animal.

78 (488)

The daily curve of nitrogen elimination in the pregnant, as compared with the non-pregnant dog.

By **J. R. MURLIN.**

Comparison of the daily nitrogen output in periods of three hours in pregnant dogs as compared with the same dogs non-pregnant, on the same diet and living under identically the same conditions, shows that the form of curve is essentially the same in the two conditions. In the pregnant condition the total curve runs below that of the non-pregnant condition at a fairly uniform distance, showing that the retention for the embryos and auxiliary structures is fairly uniform from hour to hour.

79 (489)

Contraction of muscle during voluntary innervation.

By **HORATIO B. WILLIAMS.** (By invitation.)

[*From the Department of Physiology, Cornell University Medical College.*]

This communication is a preliminary report of studies on the frequency of contraction of voluntary muscle under voluntary innervation.

The muscles studied were the flexors of the forearm, and the problem has been approached from three directions:

1. The frequency of the action currents.

2. The frequency of the sound accompanying muscular contraction.

3. The frequency of the mechanical variations over the surface covering the contracting muscles.

The action currents were registered photographically as excursions of the quartz "string" of a large Einthoven galvanometer, and the results are in consonance with those of Piper, who found the rate to be 47 to 50 variations per second.

The muscle sound was made to register itself as electrical variations by use in connection with the galvanometer of a very delicate microphone, carefully protected against external vibrations and connected with a stethoscope placed over the contracting muscles.

The rate of the sound as so determined is from 46 to 52 per second, which agrees fairly well with the rate obtained by the preceding method.

Unless great care is exercised to allow free ingress and egress of air to and from the stethoscope, large waves of frequency, 10 to 13 per second, complicate the sound record.

The mechanical movements were registered in the usual manner with receiving and recording tambours and also with a small telephone applied to the flexor surface of the forearm and connected with the galvanometer. This is an extremely delicate method of registering mechanical movements.

The frequency obtained over contracting muscles was about 12 per second with both methods.

Using the telephone method, curves of similar character and frequency were obtained over the surface of the resting arm during electrical stimulation of the flexor group of the other arm, and also for a short time following such stimulation.

These movements were also readily evoked in the resting arm during voluntary contraction of the flexors of the opposite arm.

The records of the action current do not show variations of the slow rate when the galvanometer is so adjusted as to give an optimum record of the 47 to 50 rate, but slow variations appear on increasing its sensitiveness.

It appears as a result of this study, that in voluntarily contracting muscle there are two distinct sets of rhythmic phenomena. One, occurring at the rate of 47 to 50 per second and due to voluntary impulses from the central nervous system; the other, reflex and occurring at a rate of from 10 to 13 per second. It appears extremely probable that the latter are variations in tonus.

80 (490)

Filtration through collodion sacs.

By EDNA STEINHARDT.

[*From the Hygienic Laboratory, University of Michigan.*]

Toxins, ferments, and protein solutions have been filtered through collodion membranes by many investigators but the results have varied to a considerable degree. The following experiments may explain this variation.

Collodion sacs were made and mounted on glass tubes, according to the Novy technique. Before filtration, the empty sacs were immersed in water and submitted to air pressure (three inches of mercury); if perfect, they were then used. The filtration was done under a 2-inch vacuum. After the filtration the sacs were again retested by air pressure. If still perfect, the filtrate was then used for experimentation.

In this manner diphtheria toxin was filtered. One hundredth of a cubic centimeter of this toxin killed a guinea-pig in 39 hours. Three cubic centimeters of the undiluted toxin were filtered through a collodion sac, and one hundredth of a cubic centimeter of this filtrate killed in 38 hours, none of the toxin having been held back by the filter. However, if the toxin was diluted, 1 to 100 before filtration, one cubic centimeter of the filtrate failed to kill, causing only slight induration.

When dilute cobra venom was filtered, all toxicity was lost. On filtering successive quantities of this venom through the same collodion sac, the filtrate gradually became toxic, until the fourth filtrate was practically of the same strength as the control.

This result is in accord with the work of Marbé (*Compt. rend. Soc. de biol.*, 1909, lxvii, 809) on the filtration of agglutinins through collodion sacs, and also with the passage of complement through a Berkefeld filter, as shown by me (*Jour. Med. Research*, 1904, xiii, 409), and later found by Muir and Browning (*Jour. of Path. and Bact.*, 1909, xiii, 232) working on the same subject. Evidently filtration through collodion sacs, as through the Berkefeld filter, is a phenomenon of adsorption, the substances in solution passing through when adsorption has reached a certain degree.

By altering the concentration, the quantity to be filtered, and

the thickness of the sac, results may be obtained varying from total retention to complete passage of the active substance.

81 (491)

The activation of pancreatic extract.

By **A. R. DOCHEZ.**

[*From the Laboratory of the Rockefeller Institute for Medical Research.*]

Many years ago Heidenhain demonstrated that the pancreas does not contain trypsin in an active form, but that it exists in the pancreatic tissue as a proferment or zymogen. Heidenhain was able to convert pancreatic zymogen into active trypsin by treating pancreas with weak acids. This fact was later confirmed by other investigators. Hekma, who used pancreatic juice obtained from a fistula, observed that the trypsinogen of the juice cannot be activated by treatment with acid. In 1899, Pawlow and Schepowalnikow discovered, in the mucosa of the small intestine, a specific substance which converts trypsinogen into active trypsin, and which activates both pancreatic extract and pancreatic juice. Vernon, in a series of papers published in 1901 and 1902 studied the activation of trypsinogen. His observations were largely upon pancreatic extract, although in some instances he used pancreatic juice. His conclusions are as follows: fresh pancreas shows no enzymotic activity; upon standing a few days extracts suddenly develop nearly their maximal tryptic activity; the addition of small quantities of active pancreatic extract increases enormously the rate of conversion of zymogen into active enzyme; fresh pancreas treated for twenty hours with 0.2 per cent. acetic acid develops active trypsin. Using dog's pancreatic juice, Vernon claims that one per cent. active pancreatic extract liberates three times more trypsin than one per cent. succus entericus. The same result is obtained with glycerine extract of fresh pancreas. Bayliss and Starling, who worked with large quantities of exceptionally pure pancreatic juice, contradict Vernon's results upon the activation of pancreatic juice by any other agent than the enterokinase of succus entericus. They were not able to activate the trypsinogen of the juice with active trypsin, or by means of any simple chemical

agent. They, therefore, look upon the activation of trypsinogen in pure pancreatic juice by enterkinose as absolutely specific. Larguier des Baucels, Delezenne, and Wohlgemuth have been able to activate the trypsinogen of pancreatic juice with a limited number of substances other than enterokinase. From this short historical sketch, one sees that though trypsinogen of fresh pancreatic extract can readily be activated by a large number of substances, trypsinogen of pure juice is activated with but few agents other than enterokinase.

It is well known that pancreatic juice when secreted is strongly alkaline. In the course of the experiments here detailed, it has been found that when fresh pancreas is brought in contact with alkali, the activation of trypsinogen cannot be obtained by the use of agents which are capable of activating fresh pancreas. In short, the alkali-treated pancreas resembles pancreatic juice in regard to its behavior toward activators.

Fresh normal pancreas of the dog was allowed to stand on ice in one flask in a concentration of 0.2 per cent. acetic acid; in another, at neutral reaction, and in a third, in a solution of 0.2 per cent. sodium hydrate. After twenty-four hours, the acid and alkali were carefully neutralized and the proteolytic activity of the mixtures tested in acid, neutral and alkaline medium. Degrees of digestion are expressed in terms N/10 H_2SO_4. Bacterial growth was prevented by the addition of toluol. The same quantity of pancreas was used in all experiments. The duration of digestion was, in every instance, twenty-four hours at 37° C. Beef serum denaturalized by heat served as substrate.

Medium.	Treated with 0.2 per cent. acetic acid.	Untreated.	Treated with 0.2 per cent. sodium hydrate.
0.2 per cent. acetic acid	11.0 c.c.	12.4 c.c.	0.2 c.c.
Neutral	16.4 "	4.8 "	0.9 "
0.2 per cent. sod. carb.	11.2 "	0.6 "	0.3 "

In this experiment, treatment with 0.2 per cent. acetic acid has developed proteolytic activity in all media. In untreated pancreas maximum proteolysis is observed in acid medium, and only slight proteolysis in neutral. In all portions of pancreas coming in contact with alkali, proteolysis has been paralyzed. This is especially marked in that portion of pancreas pretreated with 0.2 per cent. sodium hydrate.

In another experiment fresh dog's pancreas was inactivated by treatment with 0.2 per cent. sodium hydrate as above. The sodium hydrate was neutralized, and an attempt made to activate the alkali-treated pancreas with various agents. The inactive pancreas was allowed to stand for twenty-four hours at 37° C. in contact with the substances used for activation, and proteolysis was subsequently tested in acid, neutral and alkaline medium. The quantities of pancreas used and the technic were the same as in the experiment described above.

Activation of Pancreas Inactivated by Treatment with 0.2 per cent. Sodium Hydrate.

Medium.	Substances used for activation.				Heated pancreas.
	0	Enterokinase.	0.2 % acet. ac.	Active pancreas.	
0.2 % acetic acid	0.5 c.c.	8.8 c.c.	1.2 c.c.	0.0 c.c.	0.8 c.c.
Neutral	0.5 c.c.	19.0 c.c.	2.6 c.c.	0.9 c.c.	2.3 c.c.
0.2 % sodium carbonate	0.6 c.c.	21.5 c.c.	0.9 c.c.	0.1 c.c.	0.8 c.c.

From this experiment it is observed that pretreatment of fresh pancreas with 0.2 per cent. sodium hydrate completely prevents subsequent proteolysis. The enzyme of alkali-treated pancreas is, however, not destroyed inasmuch as it can subsequently be activated by the addition of enterokinase. Acetic acid (0.2 per cent.) which readily activates fresh pancreas is not able to effect to any appreciable extent activation of pancreas treated with alkali. Active pancreatic extract, Vernon's most effective agent for activating inactive pancreatic extract develops no activity in alkali-treated pancreas.

From these results it would seem that the activating effect of acid and the inactivating influence of alkali upon fresh pancreas do not represent a direct action upon the proteolytic zymogen, but probably exert their influence through the destruction of secondary substances which are necessary for the preservation of enzymotic equilibrium. The suggestion is made that the enzyme complex upon coming in contact with the alkaline reaction of the pancreatic juice undergoes a change analogous to that observed in the treatment of fresh pancreas with alkali, so that it is no longer readily activated by any agent other than the enterokinase of succus entericus.

82 (492)

Experiments bearing on the nature of the karyokinetic figure.

By **T. H. MORGAN.**

In the three following ways the results of centrifuging the egg of *Cerebratulus* throw light on the nature of the karyokinetic figure.

1. If the egg is centrifuged when the polar spindle is present, the spindle may be carried bodily, without injury to its rays, to the center of the egg, in those cases where the yolk is driven into the region occupied by the polar spindle. If the centrosomes are centers of force, we must suppose that these centers produced at each state in the migration of the spindle new rays and a new spindle. This seems highly improbable when the time usually taken for the formation of the rays is considered. The same reasoning applied to the central spindle would lead to the conclusion that its rays, too, are continually reformed during the migration.

2. When the basic granules of the egg are driven into the region of the segmentation spindle, the granules become arranged along the alveoli through which the rays also pass, and assuming a bead-like arrangement may obscure the rays. Lillie has advanced this evidence as demonstrative of the center of force hypothesis. My observations lead to the opposite conclusion; for I find no evidence that these granules replace the fibers. Whether the granules by changing their nature become incorporated into the polar rays is another question that must be left open at present, but even if they do so, this does not prove the center of the force hypothesis.

3. When the asters of the segmentation spindle become attached to the male and female pronuclei, they may be carried to the light pole when their nuclei are transported to that region. The fibers are often thrown into spirals, which fact is difficult to explain on the center of force hypothesis.

83 (493)

The non-production of sugar from tyrosin and glucosamin in phlorizin glycosuria.

By **A. I. Ringer** and **Graham Lusk**.

Experiments in dogs with phlorizin glycosuria show that there is no increased sugar output after ingestion of tyrosin and glucosamin.

SCIENTIFIC PROCEEDINGS.

Abstracts of the Communications,

Thirty ninth meeting.

Sheffield Biological Laboratory, Yale University. May 18, 1910.
President Morgan in the chair.

84 (494)

An examination of Fröhlich's theory of the treppe.

By **Frederic S. Lee** and **E. N. Harvey.**

[*From the Department of Physiology of Columbia University, at the College of Physicians and Surgeons, New York.*]

It is commonly believed that during the treppe a muscle possesses a progressively augmented power of performing work. According to Fröhlich, the augmentation is not real but only apparent. He believes that fatigue of the muscle elements begins with the beginning of the series of contractions, and that, from the first, it is manifested by a slowing of relaxation, a diminution in the extent of contraction, and a diminution in irritability. Successive elements of a stimulated muscle contract successively and those first in contraction begin their relaxation before later elements have reached the maximum of shortening. Since the total amount of shortening of the whole muscle represents the algebraic sum of the amounts of shortening of the several elements, with the slowing of relaxation, the total amount of shortening is increased. This more than counterbalances the diminution in the extent of contraction. The treppe is thus a physical expression of delayed vital processes and signifies a diminished, rather than an increased working power. Fröhlich has extended this theory to the augmentation observed in the preliminary stages of the action of cold, asphyxia, carbon dioxide, alcohol and other narcotics on various tissues, in the central nervous system under various conditions, in the current of action of nerves, and even in the production of heat in fevers. His theory conflicts with the theory advanced by the present senior author, according to which the

treppe represents increased irritability and increased working power, due to the action of small quantities of carbon dioxide, lactic acid and, possibly, other fatigue substances.

If Fröhlich's theory be correct, there should be a progressive increase in the length of the successive muscle curves throughout the treppe. This is found not to be so. When a muscle lever is made to close an electric circuit automatically at the precise end of each relaxation and thus to stimulate the muscle anew, it is found that the length of the muscle curves at first increases and then decreases, while the treppe is still proceeding. This fact does not seem explicable by Fröhlich's theory, but is what might be expected if the treppe were due to the augmenting action of fatigue substances.

Fröhlich's theory demands that the irritability of the muscle should progressively decrease from the time of the first contraction. This also is found not to be so. When the irritability of the excised and non-curarized muscle, as indicated by the threshold of stimulation, is determined at intervals throughout the course of the treppe, it is found that the irritability progressively increases. This again is in harmony with the theory of the treppe, proposed by the senior author.

85 (495)

An attempt to discover the cause of the specific dynamic action of protein.

By **GRAHAM LUSK.**

[*From the Physiological Laboratory of the Cornell University Medical College at New York.*]

The writer has shown that if glutamic acid be given to a phlorhizined dog three of its carbon atoms are converted into glucose. One can write the reaction thus:

$$2HOOC \cdot CH_2 \cdot CH_2 \cdot CHNH_2 \cdot COOH + 2HOH = 2CH_3\,COOH + C_6H_{12}O_6 + 2NH_3.$$

Rubner sought to explain the increase in heat production which followed meat ingestion—its *specific dynamic* action—by the supposition that protein could be used for the vital activities of the cells only in so far as it was converted into dextrose; all the oxidations of other portions of the protein yielded free heat within the

organism which could not be used as power for the living mechanism. If this were true then a considerable increase in the output of carbon dioxide would follow the administration of glutamic acid superimposed upon a regular standard diet. Alanin, which Ringer and the writer have shown to be completely convertible into dextrose, should show no specific dynamic action, whereas tyrosin with its many cleavages before it reaches a stage for use in metabolism might show a pronounced increase in carbon dioxide output.

From the experiments at hand no specific dynamic action can be shown even after giving large quantities of amino-acids, and there is not even a rise in carbon output which can be interpreted as due to "Darmarbeit" or intestinal work in the sense of Zuntz. The "standard diet" was given in two portions daily and consisted in

	Grams.	Grams C.
Cane sugar	100	42.1
Fat (+ fat in meat)	21.0	16.0
Meat (1 g. N)	33.4	3.3
Total C		61.4

The results are given in the following table. The dog was kept at a temperature of 30° C. in the chamber of a Pettenkofer-Voit respiration apparatus for a period of about 22 hours daily.

Date.	Ingesta.	N in urine.	C in respiration.
1908			
1, XII	Dextrose, 40 g.	3.55	46.56
2	" 20 g. +alanin 15.9 g. (2.5 g. N)	6.39	47.13
1910			
21, IV	Standard diet	2.02	64.25
22	" " +24 g. glutamic (2.28 g. N)	3.58	59.00
	" " in interim		
28	" "	1.68	57.72
29	" " +24 g. tyrosin (2.03 g. N)	2.78	58.02
	Interim, fasting, ordinary diet, standard diet		
13, V	Standard diet	1.19	59.24
14	[1] " " +40 g. glutamic (3.82 g. N)	3.90	57.78
15	" "	2.24	54.31
16	" " +35 g. glutamic (3.41 g. N)	3.32	52.25
17	" " +30 g. glutamic (2.85 g. N)	4.25	58.88

[1]Small amount vomited (containing 0.2 g. N).

86 (496)

A modified method for the clinical estimation of pepsin.

By **WILLIAM C. ROSE.** (By invitation.)

[*From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven, Connecticut.*]

A globular preparation well adapted for the purposes of the Jacoby-Solms pepsin test can be made cheaply from the ordinary garden pea, *Pisum sativum*.[1] This protein dissolves practically completely in ten per cent. sodium chloride solution, and after slight acidification with hyrochloric acid, yields a turbid solution. For the estimation of pepsin, 0.25 gram globulin of the pea is dissolved in 100 cubic centimeters of ten per cent. sodium chloride and filtered. One cubic centimeter portions of the clear filtrate are introduced into a series of small test-tubes, and each portion treated with one cubic centimeter of 0.6 per cent. hydrochloric acid. After the development of the turbidity, increasing amounts (0.1 to 1.0 cubic centimeter) of neutralized, five-times-diluted gastric juice are added to the tubes. Boiled, diluted gastric juice is then added until the volume in each tube is 3.0 cubic centimeters. Digestion is allowed to go on for fifteen minutes in a water-bath at a temperature of 50°–52° C. The enzyme content is expressed by the number of cubic centimeters of the standard protein solution that would be digested until perfectly clear by one cubic centimeter of the undiluted gastric juice, under the standard conditions of time and temperature.

The advantages of the modification over the original Jacoby-Solms procedure are: first, the reduction of the time necessary for the determinations—from three hours to fifteen minutes; second, the use of a perfectly non-toxic substrate; and third, the estimation of the proteolytic activity independently of the variations in acidity, thus eliminating an error in the original method.

[1]The method of preparation of the globulin together with a detailed description of the modified pepsin test will appear in an early issue of the *Archives of Internal Medicine*.

87 (497)

The metabolism of the purines in man.

By **LAFAYETTE B. MENDEL** and **JOHN F. LYMAN.**

[*From the Sheffield Laboratory of Physiological Chemistry, Yale University.*]

Adenine, guanine, hypoxanthine and xanthine were fed at intervals to two subjects living on a constant purine-free diet. The effects of the administration of these purines (1 to 1.5 grams) on various metabolic functions, especially the partition of nitrogen in the urine, was reported. The output of urinary purines is summarized here:

	Purine fed.	Nitrogen in purine nuclens fed grams.	Increase in nitrogen eliminated as			
			Uric acid.		Purine bases.	
			gram.	per cent.	gram.	per cent.
WWH	Hypoxanthine,	0.387	.248	64	.015	4
	Xanthine,	0.369	.196	53	.009	2
	Guanine,	1.114	.347	31	.037	3
	Adenine,	0.414	.153	37	.015	3.6
JFL	Hypoxanthine,	0.387	.219	56	.009	2
	Xanthine,	0.369	.170	46	.004	1
	Guanine,	1.114	.217	19	.030	2.7
	Adenine,	0.414	.126	30	.014	3

From the numerous data reported, the authors conclude that all of the familiar purines may lead to an increase in exogenous uric acid in the urine of man, with (quantitatively) little influence on the elimination of purine bases. In contradiction to the recent suggestion of Plimmer, Dick, and Leib,[1] they interpret their protocols to support the view that uric acid is a stage in the metabolism of exogenous purines, rather than an expression of leucocyte metabolism.

88 (498)

The distribution of blood in shock.

By **E. P. LYON** and **J. L. SWARTS.**

[*From the Physiological Laboratory of St. Louis University.*]

An effort has been made to determine the percentage of blood in different organs before and after shock. About fifteen animals

[1] *Jour. of Physol.*, 1909, xxxix, 98.

(dogs) have been used so far. Under Grehant's anesthetic, the arterial blood pressure was determined. Then, under conditions of high blood pressure, certain organs, or parts of organs, were suddenly ligatured or clamped off from the circulation, and then removed with their blood content. The animal was then allowed to go gradually into a state of "shock" (for our purposes, indicated by a low pressure) or was rapidly reduced to that state by concussion or burning. Then companion organs or parts were similarly clamped off and excised. The organs were weighed, cut up into fine pieces and extracted, the blood content being determined by Welcker's method. In taking the abdominal organs, we usually proceeded in the following order: (1) a small loop of intestine clamped off or ligatured suddenly, avoiding large arteries and veins; (2) a portion of one lobe of the liver, using a large clamp suddenly applied; (3) one pole of the spleen, (4) one kidney. After "shock" the same order was followed. So far, in most of our work the same animal has served for "before" and "after" determinations. This perhaps introduces doubt as to the condition of abdominal organs if shock were produced before opening the abdomen. We shall extend the experiments with variations as soon as a large series of "before" percentages is available for averaging.

Results.—Leg: three experiments; less percentage of blood after shock in all.

Thyroid: two experiments; less after shock in both.

Intestine: six experiments; less after shock in four cases; more in two. These two were early experiments, in which we were not so careful to exclude large vessels.

Liver: seven experiments; less after shock in six cases; more in one. The one case is doubtful, as 52 per cent. of blood was indicated, probably due to an error in weighing or other manipulation.

Spleen: eight experiments; less after shock in seven; equal in one.

Kidney: nine experiments; less after shock in eight; more in one.

The differences are often extreme. In one case the kidney excised before shock contained six times as much blood as its companion excised after shock.

It seems that the anemic condition always observed in the skin in shock is also found in the organs generally. Further experiments are being performed to ascertain the location of the blood.

89 (499)

The fundamental conditions of surgical shock.

By **YANDELL HENDERSON.**

[*From the Physiological Laboratory of the Yale Medical School.*]

Death in shock may be either from failure of respiration, or from failure of the circulation. In Crile's experiments, and in my own, the former mode of death was much more common than the latter. As I have recently shown, deaths of this type occur also in human beings after intense pain. The excessive breathing induced by pain diminishes the carbon dioxide content of the blood and tissues. This acapnia is the cause of the depression of all functions so characteristic of shock. Finally, apnœa vera occurs in exactly the same manner as in a normal man after voluntarily forced breathing.

If death from apnœa is prevented by supplying artificial respiration, as in the majority of Crile's experiments, or by continual afferent irritation, as in my own, the circulation fails. Crile proved that this is not heart failure. Seelig and Lyon have proved that it is not vaso-motor failure, but that on the contrary the peripheral arteries are in intense constriction. Malcolm has suggested that the volume of the blood is diminished because of a passage of serum into the tissues. Sherrington and Copeman observed a considerable increase in the specific gravity of the blood even before arterial pressure had fallen to a low level. The balance between the water content of the blood and of the tissues is probably in part dependent upon their relative carbon dioxide contents. Acapnia may alter the tonus of the veins, or the relative osmotic pressure of the blood and the tissue fluids, or the imbibition tension of the colloids of blood and tissues. *Thus acapnia diminishes the volume of the blood.*

I find that acapnia induced by excessive artificial respiration, or by excessive natural breathing during stimulation of afferent nerves (*i. e.*, trauma), involves a lowered venous pressure and

diminished diastolic filling of the heart. This condition I would call acapnial oligæmia, or exsanguinity. It is compensated temporarily by constriction of the arterioles. The blood stream diminishes until finally it is insufficient to supply the oxygen needed by the tissues. Then tissue asphyxia, and acute acidosis quickly result. The colloids of the tissues in asphyxial acidosis imbibe water in the same manner as does fibrin when soaked in dilute acid. The vascular system is thus emptied as if by hemorrhage. Fluid passes from the blood into the tissues almost as fast as it can be supplied by intra-venous infusion of saline.

Thus there are two sequences: (1) pain-hyperpnœa, acapnia, and fatal apnœa vera, *i. e.*, failure of respiration; (2) pain-hyperpnœa, acapnial oligæmia, and cyto-asphyxial oligæmia, *i. e.*, failure of the circulation because of exsanguinity.

A full discussion of this topic and its literature will soon be published in the *American Journal of Physiology*.

90 (500)

Observations on the nature of the antitrypsin of the serum.

By **R. WEIL** and **S. FELDSTEIN.**

[*From the Department of Experimental Therapeutics, Cornell University Medical School, New York.*]

In a previous communication to this society, it was shown by the authors that the viscosimeter offers a method for determining the anti-tryptic activity of serum which is extremely accurate, delicate and constant in its results. Further study by means of this method has revealed the fact that this so-called anti-tryptic activity is in reality very much more complex than had hitherto been suspected. If a series of intracellular enzymes are prepared from various human organs and from carcinomata, according to the method of Wiechowski, by drying, it becomes possible to test the inhibitory action of any given serum against each of these enzymes by the use of the viscosimeter. This has been done by the authors with a considerable number of sera. The resulting figures, which have been constant in successive experiments, demonstrate that the inhibitory value of each serum is distinct and different for each of the enzymes tested. These differences are extreme, inasmuch

as a given serum may show an inhibition of only five per cent. of the total digestion against one organ enzyme, and as much as 95 per cent. against another. With a second serum, again, these relations are found reversed. It seems impossible to interpret these results otherwise than as indicative of the existence of a variety of ferments, each one more or less characteristic of the organ from which it is derived. This multiplicity of proteoses has recently been suggested by Vernon as the probable explanation of certain differences shown in comparative digestion experiments with the pressed juices obtained from the various organs. At the same time, it seems necessary to assume the existence in the serum of a corresponding variety of anti-ferments.[1] It is, therefore, evident that it is impossible to speak of the "anti-tryptic" activity of serum, inasmuch as this term comprises a heterogenous set of functions. An observation which will prove to be of interest, if confirmed by a wider series of experiments, is the fact that sera derived from cases of cancer have hitherto shown a characteristic mode of reaction. Their inhibitory activity against commercial trypsin has in general been very high, as previously determined by many German observers, by the casein method of Gross; in some cases it has been normal or average; in others, very low. In no case, however, has the inhibition exercised by any cancer serum against the "tryptic" ferment derived from a cancer notably exceeded its inhibition of trypsin; in almost all cases it has fallen enormously below the latter. In the normal control cases, these relations have hitherto been exactly reversed. An explanation for these facts the authors do not consider possible as yet. At all events, the viscosimeter seems to afford a simpler method than any yet devised to determine these complex relations of the serum.

[1]Whether the inhibitory activity of the serum is in reality attributable to true anti-ferments cannot be discussed here, but to the authors this seems the only likely explanation of certain conditions, in spite of the fact that Hedin was able to reproduce some of the phenomena of inhibition by the use of charcoal.

91 (501)

On the power of reproduction without conjugation in Paramecium.

By LORANDE LOSS WOODRUFF.

[*From the Sheffield Biological Laboratory of Yale University.*]

I have presented to this society the results obtained to May, 1909, on the life cycle of *Paramecium* when subjected to a varied environment. This communication brings the results up to date (May 18, 1910).

A culture of *Paramecium aurelia* was started May 1, 1907, by the isolation of a "wild" individual from a laboratory aquarium, and it has been under daily observation during the thirty-six and a half months which have elapsed since that time. Infusions of hay and grass, together with any material that may be found in the usual habitat of *Paramecium*, have been employed as a culture medium. The possibility of infecting the culture with "wild" strains has been avoided by boiling the infusion. Daily isolation of an individual from each of the lines of the culture has prevented the possibility of conjugation taking place, and has enabled me to obtain an accurate record of the division rate.

So far the culture has attained the 1,795th generation. The average rate of division for the thirty-six and a half months has been more than one and a half divisions per day. The average rate for any ten-day period has not fallen as low as one division in two days, while it has been for several ten-day periods more than two and a half divisions per day. Therefore, since marked physiological depression has not been indicated by the division rate, special stimuli have not been resorted to at any time to "rejuvenate" the culture.

The results derived up to the present time from the study of this culture show that under the conditions of a suitable, varied environment *Paramecium aurelia* does not necessarily undergo "cyclical" changes in general vitality, and give strong reasons for believing that the life history of this organism may be of unlimited duration without conjugation or artificial stimulation.

92 (502)

Alleged rhythm in phototaxis synchronous with ocean tides.

By **MAX WITHROW MORSE.**

[*From the Harpswell Biological Laboratory, South Harpswell, Maine.*]

A series of observations upon the periwinkles, *Littorina litorea* and *Littorina rudis*, and the snail, *Ilyanassa obsoleta*, carried on from June 18 until August 26, failed to corroborate the conclusions of Bohn,[1] who describes a daily rhythm in the reaction to light in specimens of *Littorina litorea* and *Littorina rudis* corresponding to the times of high and low tide, even when the animals are taken from the sea and placed in aquaria, exhibiting thus a sort of "memory" of the tides.

In the present experiments the reaction to light was tested in each specimen, at least three times a day, and white and black screens were used, as in Bohn's experiments, to determine whether the forms were positively or negatively phototactic. During the days of June, they were, as a rule, negatively phototactic, and as night approached, they became positively phototactic. However, after July 18, the preponderance of positive phototaxis during the day was very noticeable. This period of transition corresponded to the time of change from spring to neap tide, during which the specimens out on the rocks were exhibiting a corresponding change in phototaxis, for the water did not reach them; their behavior tallied with the description of Mitsikuri,[2] who showed that when desiccated, periwinkles became positively phototactic, and when wet, turned negatively phototactic. In these observations there is an approach to Bohn's conclusions concerning rhythms in phototaxis with respect to *fortnightly* (spring and neap) rhythms in tides, if not to his conclusions concerning daily (high and low) oscillations. However, no other period was passed through while these animals were under observation, during which there was a return to *negative* phototaxis, and it is doubtful that this change was anything more than a variation in laboratory conditions which were not determined by suitable check. On the

[1]Bohn, Georges, *Compt. rend. d. l'Acad. des sciences*, 1904, cxxxix, 610, 646.

[2]Mitsikuri, K., *Annot. zool. japonenses*, 1901, 4.

other hand, Bohn states that the rhythm disappears after a time, in laboratory specimens and my failure to observe anything farther indicating a change in phototaxis may be due to the disappearance of the rhythm from the animals. Details of the experiments are published in another journal.

93 (503)

The vaso reaction of hydrophobic rabbit blood serum in dogs.

By **J. P. ATKINSON** and **C. B. FITZPATRICK.**

[*From the Chemical and Research Laboratories of the New York Department of Health.*]

In November of last year we injected into the femoral vein of a dog 5 c.c. of the defibrinated centrifuged blood of a rabbit, which had previously been injected subdurally with a fixed seven days' virus of hydrophobia.

The arterial pressure taken with a mercurial manometer from the carotid artery showed a marked depression. Further trials of the same experiment gave the same results. Since these experiments, we have been able to demonstrate that the blood serum of rabbits, which have been infected with hydrophobia 72 and 48 hours previously as described, possess this depressor substance, and even in the serum of a rabbit which had been infected only 24 hours previous to bleeding, there was a decided indication of a depressor substance.

If the blood of a rabbit suffering from hydrophobia be run into absolute alcohol and the filtered alcoholic extract be evaporated on the water-bath or *in vacuo*, there will be found a water-soluble substance which causes a marked arterial depression. We obtained this depressor effect in the alcoholic extract also from the blood of the rabbits injected only 48 and 24 hours respectively before the test.

Choline is a poisonous nitrogenous base derived from the phosphorized fat of neucleo-protein, in which brain and nerve tissue are very rich. It has been demonstrated that hydrophobia travels along the nerve from the point of injection to the brain. It seems to us quite possible that in the development of the disease neucleo-protein is decomposed; among its decomposition products choline

finds its way into the blood stream. In such case it would naturally act as an auto-intoxicant and would be one of the factors in the death of the animal.

A number of years ago one of us attempted on this assumption to isolate choline from the blood of a hydrophobic rabbit. The amount of blood taken was not more than 30 c.c. and the result was negative.[1] We have repeated this attempt on larger quantities of blood. The blood of three rabbits inoculated 7 and 8 days previously with the fixed virus was run into absolute alcohol. The alcoholic extract was filtered off and evaporated to dryness at a low temperature. Platinic chloride was added in the manner recommended for the production of choline platinic chloride crystals. The precipitate obtained was examined under the microscope. It was made up of six-sided yellow crystals, a large part of which were in plate form. There were not sufficient crystals to determine the per cent. of platinum.

Thus far it would appear that in hydrophobia, as in certain other diseases, where there is destruction of nerve tissue, choline is one of the split products. A number of other experiments are being carried out to check and amplify these results.

Last year Dr. Poor, of the Research Laboratory, and one of us attempted to protect rabbits from hydrophobia by means of injections of atropine, which antagonizes choline on the assumption that choline was present in the blood of rabbits with hydrophobia.[2] The results were unsuccessful but have been undertaken again under a different system. The results of this second attempt will be published later.[3]

[1]J. P. Atkinson, in 1903, unpublished.

[2]J. P. Atkinson, unpublished.

[3]Since these results were presented the following experiment was made: The blood of a normal rabbit, which had been 72 hours previously injected subdurally with an emulsion of normal brain substance was run directly into absolute alcohol and the rabbit immediately autopsied. The autopsy showed signs of considerable necrosis and inflammation at the point of injection. The filtered alcoholic extract of this rabbit's blood was evaporated to dryness at a low temperature and mixed with physiological salt solution. This mixture was injected into the femoral vein of a dog and the arterial pressure as taken with the mercurial manometer from the carotid artery showed a marked depression. Five cubic centimeters of the clear defibrinated serum of this blood also caused a marked depression.

94 (504)
The precipitation of diphtheria antitoxin by means of precipitins.

By **J. P. ATKINSON** and **E. J. BANZHAF.**

[*From the Chemical and Research Laboratories of the New York Department of Health.*]

This work was undertaken partly to check and to review the previous observations by one of us a number of years ago on the precipitation of diphtheria antitoxin from solutions by means of antibodies prepared by injecting diphtheria antitoxic globulin and globulin of normal horse serum into rabbits,[1] partly to determine whether such a method could be used in the further purification of diphtheria antitoxin.

In these earlier experiments it was found that the antibody formed by the injection of globulin of normal serum into rabbits threw out of solution diphtheria antitoxin just as well as the antibody formed by the injection of diphtheria antitoxic globulin.

We undertook these last experiments with the purest diphtheria antitoxin fractionated from the globulin, and serum globulin fractionated in the same way and under the same conditions. The sera were kept at 56° C. for fifteen hours to convert, as far as possible, pseudo-globulin into eu-globulin. The diphtheria antitoxin under these conditions remains unchanged with the pseudo-globulin.[2] The solution was then half saturated with ammonium sulphate and the precipitated globulin filtered off. The precipitate was washed with saturated sodium chloride to remove the pseudo-globulin. The sodium chloride solution was precipitated with acetic acid and again filtered and squeezed between filter paper to remove excess of salts, especially ammonium sulphate, and finally dialyzed to free it as completely as possible from salts. Putrefaction was prevented by the presence of chloroform. The dialyzed globulin in the case of the diphtheria antitoxin was highly concentrated and is the antitoxin of commerce today.

Both sera, antitoxic and normal, were put through exactly the same process in preparing the globulin for injection.

[1] J. P. Atkinson, *Med. News*, 1904, lxxxiv, 375.

[2] Banzhaf, *Proc. of the Soc. for Exp. Biol. and Med.*, 1908, vi, 24.

Injections and development of antisera.—Nine rabbits were immunized against diphtheria antitoxic globulin and eight against normal serum globulin as follows:

Antitoxic globulin, preparation No. 163.

Injections begun March 7, 1909. Three rabbits injected at intervals of three days.
No. 1—4 injections of 2.5 c.c. produced an immune serum of 1/20,000 strength.
No. 2—6 injections of 2.5 c.c. produced an immune serum of 1/20,000+ strength.
No. 3—9 injections of 2.5 c.c. produced an immune serum of 1/30,000+ strength.

Injections begun May 1, 1909; 2 rabbits subcutaneously.

5 injections, each of 2.5 c.c. every 2 days.

Injections begun December 2, 1909; 2 rabbits.

6 injections, each 2.5 c.c.

Normal serum globulin.

Injections begun March 24, 1909; 3 rabbits injected every 3 days.

No. 1—5 injections of 2.5 c.c.
No. 2—5 injections of 2.5 c.c.
No. 3—9 injections of 2.5 c.c.

Injections begun May 1, 1909; 1 rabbit subcutaneously.

5 injections of 2.5 c.c. every 2 days.

Injections begun December 2, 1909; 2 rabbits.

5 injections each of 2.5 c.c.

The rabbits were bled ten days after the final injection. It was not considered necessary to test the strength of the immune sera after the first tests, since it was all needed for the experimental work.

Two explanations are applicable to these reactions.

1. Diphtheria antitoxin is a globulin which is not changed by heat to a form insoluble in saturated solution of sodium chloride and is consequently precipitated by a globulin antibody of the same nature. We have not yet tried the effect of the addition of an antibody for pure eu-globulin on diphtheria antitoxin.

2. Diphtheria antitoxin is carried down mechanically in the precipitation of the globulin by the antibody as a mordant carries a dye out of solution and holds it.

If the first explanation is true then the combination of the diphtheria antitoxin with the antibody is a comparatively loose one, because normal saline solution and glycerine partially separate them, and the precipitate will neutralize diphtheria toxin.

If the second explanation is true, the precipitation of the globulins by means of a precipitin acts as a very complete and powerful mordant, using the term "mordant" in the broad sense of a cleaning agent.

The table shows the results of the addition of immune antitoxic and normal globulin to diphtheria antitoxin.[1]

Preparation of diphtheria antitoxin.	Units per c.c.	Dilution with saline sol.	Immune antitoxic globulin.	Hours at room temperature.	Strength of clear centrifugalized fluid in units.[2]	Per cent. of antitoxin in units in precipitate.[2]	Precipitate extracted with distilled water in units.	Precipitate extracted with glycerine in units.[2]	Precipitate emulsified and tested in units.[2]
163	700	1 c.c. of 1/10+8 c.c.	+1 c.c.	24 hrs.	700				
163	700	" 1/100+5 c.c.	+1 c.c.	24 "	675	4	none.		
163	700	" 1/200+5 c.c.	+1 c.c.	24 "	650	7	"		
163	700	" 1/400+5 c.c.	+1 c.c.	24 "	575	18	"		
163	700	" 1/400	+6 c.c.	24 "	175	75	"		500
			Immune normal glob.						
163	700	" 1/400	+6 c.c.	24 "	175	75	"		500
			Immune antitoxic glob.						
172 B	3000	" 1/3000+	1 c.c.	48 "	300	90	"	725	1500
172 B	3000	" 1/3000+	3 c.c.	48 "	150	95	"	750	1500
			Immune normal glob.						
172 B	3000	" 1/3000+	1 c.c.	48 "	300	90	"	700	2000
172 B	3000	" 1/3000+	3 c.c.	48 "	150	95	"	300	1500
155	850	" 1/200+	No. 3 16 c.c.	48 "	40	95	"	225	500
155	850	" 1/200+	16 c.c.	48 "	40	95	"	225	500
			Gray rabbit.						
155	850	" 1/200+	16 c.c.	48 "	170	80	"	200	400
155	850	" 1/200+	16 c.c.	48 "	170	80	"	200	400

[1] Later experiments showed that the precipitate extracted with sodium chloride yielded some antitoxin. It is evident that a relatively large amount of immune serum must be added to the antitoxin to throw out the antitoxin in anything like quantitative amounts.

[2] Unit strength is calculated on the basis of the undiluted original serum.

95 (505)

Further observations on the structure of anastomosed blood vessels.

By **C. C. GUTHRIE.**

[*From the Department of Physiology and Pharmacology of the University of Pittsburg.*]

In this series of experiments the theoretical optimum conditions were fulfilled, *i. e.*, very rapid auto-grafts were made and the use of salt or other foreign solution avoided. A segment of common carotid artery interposed between the ends of a divided common carotid artery for twenty-eight days shows very slight or no alteration excepting at the lines of anastomosis where a moderate thickening occurred, due no doubt to trauma. A segment of external jugular vein similarly engrafted on common carotid artery for twenty-eight days shows a moderate and somewhat irregular thickening of the wall, but the thickening is not nearly so great as in another such experiment previously reported.[1] The intima is smooth and glistening but yellowish, particularly in the more thickened areas. The latter are very richly supplied with apparently newly formed blood vessels. Muscle fibers are almost or entirely absent. Elastic fibers are fairly abundant in the middle coats. The remainder of the tissue is more or less hyaline in appearance. The adventitial coat is the most thickened and dense, perivascular fibrosis apparently having occurred.

A very different picture is presented by an internal jugular vein and its branches in which the circulation was changed to arterial and reversed by anastomosis of the peripheral end of the vein to the central end of the common carotid artery after division of the vessels. On opening the vessel, ten months and twenty-seven days after the operation, it does not collapse as an ordinary vein. The wall is *more rigid*, thicker and more transparent. The intima is smooth and glistening. Muscular and elastic fibrous tissues are present. The plain fibrous tissue is greatly increased in amount and density, particularly in the middle and outer coats. Nutrient blood vessels are present but they are not nearly so conspicuous as in the venous segment.

[1] *Surg., Gynec., and Obs.*, 1906, ii, 266.

Without going into a detailed discussion of these structural alterations, I may say that these findings support my former view, namely, that nutritional disturbances in such vascular tissues are of fundamental importance in interpreting the results.[1] And furthermore, with our present knowledge such observations do not help to explain the nature of pathological processes such as arteriosclerosis, which result in structural alterations in blood vessels.

96 (506)

Modification of tissue oxidations in vitro.

By **F. V. GUTHRIE.** (By invitation.)

[*From the Department of Physiology and Pharmacology of the University of Pittsburg.*]

The purpose of this investigation was to determine the influence of certain substances upon oxidations by tissues *in vitro*, with a view of casting some light on the relation between such substances and tissue respiration after the administration of these substances to animals. The general method of investigation was similar to that practiced by Yeo.[2] Tissues and solutions of oxyhemoglobin of amphibians, reptiles, birds and mammals were employed. The tissues were placed in freshly prepared oxyhemoglobin solution made from fresh blood obtained from the same animal. The mixtures were made in test-tubes and for the most part air was not entirely excluded. The darkening of the hemoglobin solution as observed directly and the appearance of reduced hemoglobin as shown spectroscopically were taken as indicating the amount of reduction.

Preliminary experiments with mammalian tissues gave a value for different tissues somewhat different from that obtained by Bert,[3] who employed a different method. Also the results showed that tissues of warm blooded animals reduce such oxyhemoglobin solutions more actively than those of cold blooded animals; this observation agrees with the results of Battelli and Stern.[4] For the

[1] *Jour. of the Amer. Med. Assoc.*, 1908, l, 1035.

[2] *Jour. of Physiol.*, 1885, vi, 93.

[3] Leçons sur la physiologie comparée de la respiration, Paris, 1870, p. 46.

[4] *Jour. de physiol. et de path. gén.*, 1907, ix, 1.

later experiments muscle and liver were more extensively employed, because of their activity and their relative bulk. The tissues were prepared by cutting into gram cubes, or chopping finely, or crushing in a mortar. Both fresh and boiled extracts made from crushed tissues were studied.

It appears that the greater the area of tissue exposed, the more rapid the reduction of oxyhemoglobin. Fresh extract is slower in reducing oxyhemoglobin than the tissue itself; and boiled extract is without such effect.

The modifying influence of magnesium sulphate, magnesium chloride, sodium sulphate, sodium chloride, potassium chloride, calcium chloride, cane sugar and quinine sulphate on the reduction of the oxyhemoglobin solutions in the presence of the tissues and tissue extracts was then studied. Different concentrations of the substances were employed and as a rule reduction bore an indirect ratio to the concentration. Also some significance is attributable to the molecular character of the different salts for there are differences in the action of solutions of equal molecular concentration. But the physical character of the solution itself seems to be a very important factor. Cane sugar, calcium chloride and quinine sulphate not only exhibit a marked restraining action on the reduction of oxyhemoglobin, but they appear to favor its transformation into methemoglobin.

In general, the results indicate that reduction of oxyhemoglobin solutions under the conditions of these experiments is not a very true picture of the activities of tissues *in vivo*, for the activity varies directly with the time of removal of the tissue from the body. An extract of a perfectly fresh tissue is much less powerful than an extract of a tissue aseptically removed and preserved for a time before making the extract. In other words, the reducing property seems to be largely the result of *post mortem* changes. It seems clear that more delicate methods of experimentation are necessary for obtaining the desired information, and, therefore, another series of experiments with methods having for their object the preservation of the vitality of the tissues is now being conducted.

97 (507)

The development and function of the heart in embryos without nerves.

By **DAVENPORT HOOKER.** (By invitation.)

[*From the Sheffield Biological Laboratory of Yale University, New Haven, Conn.*]

The somatic muscle in frog embryos, from which the cord has been removed, was proven by Harrison (1904) to develop and differentiate normally. Such muscle tissue, when stimulated by an extremely fine needle point, will contract provided the needle perforates the skin and penetrates the muscle itself. The response produces a single quick bending of the body toward the side stimulated, the point of stimulation being the center of contraction. Other experiments show that the muscle tissue cannot be stimulated through non-nervous protoplasmic connections.

In frog embryos from which the entire nervous system has been removed at the stage immediately following the closure of the neural folds, the heart functions normally. The rate is, however, slightly lower than in normal individuals. Microscopic examination shows that the cardiac muscle of such embryos has differentiated normally. The condition of this tissue very closely parallels the results obtained by Harrison in somatic muscle.

The results of these experiments show that, in the total absence of the nervous system, somatic muscle is directly irritable, the heart will function normally and cardiac muscle like somatic muscle will differentiate normally.

98 (508)

The toxicity of amyl acetate.[1]

By **WILLIAM SALANT.**

[*From the Bureau of Chemistry, U. S. Department of Agriculture.*]

From four to six cubic centimeters per kilo of amyl acetate injected into frogs caused paralysis and coma in from 15 to 30 minutes. These symptoms lasted 24 hours, with final recovery. In some cases such doses proved fatal. Larger doses were in-

[1]Published by permission of the Secretary of Agriculture.

variably fatal. Experiments with 2.5 cubic centimeters per kilo administered in 2 per cent. suspension in water, failed to cause any symptons. Experiments were also made on rabbits. Amyl acetate was given by mouth in aqueous suspension or dissolved in neutral olive oil. Five cubic centimeters of amyl acetate given by mouth to rabbits weighing about 1,500 grams did not produce any symptons in any of the animals experimented upon, except one in which the dose proved fatal within 24 hours after its administration. The effect of amyl acetate on blood pressure was studied in dogs. One cubic centimeter injected directly into the circulation within 25 seconds caused a fall of blood pressure amounting to 56 per cent. When the vagi were eliminated the fall of blood pressure was still greater. In both instances there was a marked slowing of the pulse.

99 (509)

The elimination of caffein in the bile.[1]

By **W. SALANT** and **W. O. EMERY.**

[*From the Bureau of Chemistry, U. S. Department of Agriculture.*]

The elimination of caffein and its products of decomposition in the urine has been studied by a number of investigators, in dogs, rabbits and in man. Its presence in the digestive secretions has been recently made the subject of a special investigation in this laboratory. It was found in the bile removed from the gall bladder of a number of dogs poisoned with caffein. In every case appreciable quantities were found. A dog which was given 1.5 grams of caffein by mouth died four hours later. The bile removed from the gall bladder contained 4.4 milligrams of caffein. Similar results were obtained in other experiments. Experiments made on rabbits with temporary bile fistula have shown that the elimination of caffein likewise takes place by this path in these animals. Caffein was found in the bile two hours after its subcutaneous injection.

[1]Published by permission of the Secretary of Agriculture.

100 (510)

An experimental study of the resistance to compression of the arterial wall.

By **T. C. JANEWAY, M.D.**, and **EDWARDS A. PARK, M.D.**

[*From the Department of Practice of Medicine, College of Physicians and Surgeons, Columbia University.*]

The object of this study was to determine whether the resistance to compression of the arterial wall introduces an error of any importance in the clinical measurement of systolic blood pressure by methods employing circular compression of the arm.

No previous studies are free from serious criticism on the ground of inaccuracy of the methods employed. Some direct on post-mortem vessels (v. Basch, Martin, Herringham and Womack), and some indirect (Oliver, Hill, Williamson, Russell). In consequence of the discordant results, opinion has been divided. Some hold the resistance to compression of the arterial wall to be negligible; others that it might be extreme. The present study has been carried on by a method giving graphic records of the pressure within the artery, the pressure in the external compressing medium, and of the changes in the outflow from the artery by a Hürthle membrane manometer. Ringer's solution was used in all the experiments. The point of first collapse of the artery, of complete obliteration of its lumen, and of resumption of the flow on lowering the external pressure after obliteration were recorded in each experiment. The latter proved by far the most constant index and most analogous to the ordinary criterion of the return of the pulse in clinical work.

The post-mortem vessels examined gave the following results:

Ten carotids from infants.

Readings at 30, 100, and 150 millimeters internal pressure.
Difference of pressure at which flow ceased:

Maximum = 8 mm. Hg.
Average = 3.9 mm. Hg.
Minimum = 1 mm. Hg.

Twenty carotids from adults.

Number examined.	Condition.	Internal pressure = 100 mm. Hg.	Difference of pressure at which flow: Ceased.	Returned.
16	Slight atheroma.	Maximum	30	19
		Average	15	9
		Minimum	3	0
3	Moderate atheroma.	Maximum	13	9
		Average	10	5
		Minimum	6	2
1	Calcified.		28	14

These observations show clearly that, other things being equal, small arteries with thin walls are more readily compressed than large arteries with thick walls, but in no case was a higher pressure than 19 millimeters required.

Some experiments were made on the passage of a wave, showing that at the point of return of the flow a small pulse wave was transmitted through the artery.

Arteries from amputated limbs were examined in the hope that they might be obtained in a surviving state and that the effects of tonus upon the compressibility might be studied. Though examined within two hours after removal we were unable to demonstrate clearly their surviving character, so that our results with them must be considered merely corroborative of those with dead vessels.

Artery.	Length.	Difference of pressure at which flow: Ceased.	Returned.
Normal femoral.....	7.5 cm.	4	3
Normal femoral.....	7 "	11	2
Calcified post tibial.....	11 "	24	11
Extremely calcified femoral.....	8 "	28	16

These results, with the single calcified post-mortem vessel, show that the effect of even extreme calcification of the vessel is not very great, 11 to 16 millimeters being the over pressure found requisite for these vessels, which is less than the resistance found in some practically normal vessels. The evidence is, therefore, clear that other factors are of preponderating importance.

Since the study of O. B. Meyer demonstrated the extreme degree of contraction into which ox carotids pass when placed in ice cold Ringer's solution, and that such arteries, warmed and stretched to overcome this contraction, react to vaso-constrictor

substances for as long as six days, surviving ox arteries were chosen as the best material for the study of this other factor in the arterial wall, namely, tonus. These vessels were examined first cold and contractured, then warmed to body temperature, then stretched to relaxation by 100 millimeters internal pressure, then after the introduction of adrenalin, and finally of barium chloride, into the internal circulation. In each case a control tracing of the reaction of a strip of the vessel according to Meyer's method, carried under identical conditions and tested at the completion of each stage of the experiment, was made. The surviving character of the vessel was thus demonstrated.

Of 38 common carotids and 4 mesenterics from the ox, the following gave results free from obvious error:

Seven ox carotids.

	15° C.	37° C.	Stretched.	Adrenalin.	Barium chloride
Maximum	68.5	22	9.5	10.5	28.5
Average	42.8	14.3	6.6	8.9	15.5
Minimum	25	8	4.5	7.5	9

Four ox mesenterics.

Maximum	52	9	5	8	55
Average	25.1	6.5	3.8	6.6	29.5
Minimum	10.5	4	2	6	18

These observations demonstrate very clearly the relation between tonus of the arterial wall and its resistance to compression. A definite opinion as to the possible maximum effect of tonus, and, therefore, the placing of a numerical value for this factor of error, is not possible as yet.

101 (511)

A simple device for regulating the administration of ether or chloroform, with either artificial or voluntary respiration.

By **A. O. SHAKLEE.**

[*From the Department of Physiology and Pharmacology of the Laboratories of the Rockefeller Institute for Medical Research.*]

In the course of a study by Dr. Meltzer and myself of the use of continuous insufflation in the treatment of various forms of fatal poisoning, the apparatus described below was devised to simplify the control of anesthetic and pressure of air entering the

lungs. By means of this device an animal may be kept in any desired state of anesthesia over a long period of time with little or no attention.

The apparatus consists of a three-necked Wolff-bottle or other convenient container for the anesthetic, so fitted with tubes (metal or glass) and stop-cocks that by turning slightly a single stop-cock any portion or all or none of the stream of air for respiration may be passed over the surface of the anesthetic, thus charging the air with any desired quantity of the anesthetic. The relative quantity of anesthetic in the inspired air may be read off on a convenient scale. The apparatus is also fitted with a manometer, and an escape stop-cock for regulating the pressure of the air entering the lungs. The cock regulating the quantity of air passing into the bottle is a three-way cock placed at the junction of a T-tube, the vertical limb of which passes through the stopper of a side neck of the bottle. The ports of the cock are so arranged that the one admitting the air is always wide open, and the port leading into the anesthetic container begins to open as the port leading directly to the lungs begins to close. Thus any portion or all of the air stream may be shunted into the anesthetic container, and on issuing at the farther opening it rejoins, by means of a T-tube, the stream passing directly to the lungs, charging it with the desired quantity of anesthetic. The manometer is introduced into the circuit on the side of the container nearest the lungs. It is provided with a direct reading scale, visible from either side. The stop-cock for regulating the pressure is placed on the side of the container nearest the air pump. The third neck of the container is fitted with a funnel tube for filling. It is also convenient to have a side tubulure near the bottom of the container, by means of which any water condensed in the container may be off. The whole apparatus is mounted on a compact frame.

Not only was the device found useful with artificial respiration, but a preliminary trial seemed to indicate that it would also prove serviceable in administering an anesthetic with voluntary respiration either with or without tracheotomy. If it is desired to administer the anesthetic without tracheotomy, it is only necessary to introduce a tube (a stomach tube answers very well) into the trachea and attach it to the bottle. The tube in this case should

be sufficiently large to fit the laryngeal opening closely so as to prevent aspiration, and also to cause enough of the inspired air to pass through the anesthetic container. If it is desired to reduce the amount of dead space, it may be done by placing a suitable exit valve in the tube near the mouth.

If it is desired to mix a gas with the air in varying proportions, it is only necessary to place a three-way cock of the kind described at the juncture of the gas stream with the air stream.

102 (512)

Hybridization in a mutating period in Drosophila.

By T. H. MORGAN.

[*From the Department of Zoölogy, Columbia University.*]

In the fourth generation of a pedigree stock selected for the absence of a black shield on the thorax, a few individuals appeared having dark specks on the sides of the thorax below the base of the wings. Thirty-two individuals with specks appeared to 167 without specks. Again from one set of the latter a new brood was obtained that gave 19 present to 286 absent, or 1 to 15. Isolated, the new type bred true. These were mass results, and might have been due to a few individuals in the culture transmitting the specks on the wings, while the majority of the individuals might not transmit this character. Isolated females, not virgins, gave the following proportions:

Absent.	Present.
18	2
24	0
31	0
24	0
31	6

Here the results might have been due to a single female pairing to more than one male before isolation. Therefore, virgin females and males were isolated in pairs from the same stock. The following records are typical results.

Absent.	Present.	Absent.	Present.	Absent.	Present.
37	15	49	14	20	1
3	1	31	5	7	1
21	0	91	0	33	1
23	0	69	0	12	8
63	16	21	18	46	7
49	0	23	1	38	0

From a Mendelian point of view, two classes of broods are expected, if the absent type be the dominant and the present type (specks). The recessive offspring of a pair should be either all without (DD × DD or DD × DR), or 3 absent to 1 present (DR × DR). Two groups, in fact, appear; but when the specks occur, the number of individuals having them departs far from expectation in many cases.

When a fly with specks present is bred to one with specks absent the Mendelian expectation is either all with specks present (DD × RR) or half with and half without (DR × RR). The following cases show considerable departures from expectation.

Absent.	Present.
28	0
48	56
63	3
65	0

The second generation of the last combinations when 100 per cent. absent was obtained, should give the 3 to 1 proportion.

Several other mutants of these flies are under observation. A male in which the red pigment of the eye is totally absent has produced in the first generation, by his sisters, 162 red eyed to one white eyed fly. The results show that the character is germinal, but reappears at present in only a very small percentage of the first generation.

103 (513)

The chromosomes in the parthenogenetic and sexual eggs of phylloxerans and aphids.

By **T. H. MORGAN.**

[*From the Department of Zoölogy, Columbia University.*]

An examination of the ovarian parthenogenetic and sexual eggs of aphids and phylloxerans has shown that the synapsis stage is entirely omitted in the parthenogenetic eggs, both male- and female-producing; while on the other hand the sexual eggs pass through a synapsis period, *i. e.*, a period when the chromosomes contract to one side of the nucleus reappearing later in the reduced number. These observations show that the full number of

chromosomes in these parthenogenetic eggs is due to the omission of a synapsis period, and not due to a separation of the chromosomes subsequent to synapsis. Synapsis appears, therefore, to be a phenomenon associated with the union of the paired chromosomes and to have no other significance for development.

Two years ago I reported that two classes of spermatozoa are formed in phylloxerans, as in other insects, but that the male-producing class degenerates. Consequently all the fertilized eggs have the female number of chromosomes. I reported that, nevertheless, when males appear in the later life cycle, they have a smaller number of chromosomes (one or two less) than the parthenogenetic female or the sexual female. I suggested that one (or two) chromosomes must be lost in the polar body of the male egg. I can now state that this inference is correct, since I have found all stages in the separation of the daughter plates in the polar spindle of the male egg. In the telophase one double chromosome (its halves equal) is found lagging in the middle of the spindle. It passes always to the outer pole, which means that the lagging chromosome passes to a prescribed pole. The theoretical questions involved will be discussed elsewhere. The lagging chromosome lies outside of the nucleus of the polar body, sometimes in a vesicle of its own. In the female egg all of the chromosomes divide equally in the polar spindle and no lagging body is present.

104 (514)

The biological significance of the Sertoli cells.

By **F. M. HANES.** (By invitation.)

[*From the Department of Pathology, College of Physicians and Surgeons, Columbia University.*]

In the normal testicle there are three parenchymatous elements, namely, sperm-forming cells, Sertoli cells and interstitial cells. In the cryptorchid testicle only two types of cells are found, Sertoli cells and interstitial cells. The latter form the bulk of the cryptorchid testicle; the former line, in a synchtial manner, the small seminiferous tubules.

Since the genitalia of castrated animals are very atrophic and secondary sexual characters absent, while both are normally de-

veloped in cryptorchids, one can conclude, firstly, that the testicle does furnish an internal secretion to the organism, and, secondly, the secretion is elaborated either by the Sertoli cells or interstitial cells. It is the purpose of this note to bring forward evidence which has come to light in a study of normal and cryptorchid testicles of the pig, showing that the Sertoli cells have the very definite function of furnishing nutriment, especially fat, to the developing sperm-cells. Benda, Peter, Grobben, v. Ehner and others have concluded on morphological grounds that the Sertoli cells are nutritive cells; evidence from the physiological side has been lacking.

Fat is a constant physiological constituent of Sertoli cells. In the cryptorchid testicle this fat is seen to be greatly increased in amount, and ether-alcohol extractions show that whereas 18.3 per cent. of the dried weight of the normal testicle is fatty matter, 30 per cent. of the dried weight of the cryptorchid testicle is composed of fat. The sperm-forming cells are absent from the cryptorchid testicle, hence the fat accumulates in the Sertoli cells. Miescher has found that 58 per cent. of the cytoplasm of the salmon sperm is extractable by alcohol-ether.

In the normal testicle large droplets of fat are found in the base of the Sertoli cells, and as one proceeds centralward the fat in these cells is found more and more finely divided, lying in close contact with the spermatids, which also contain fat droplets.

Applying Marchi's stain to the testicle, it is found that only the large peripheral droplets reduce osmic acid; the smaller centrally disposed droplets remain uncolored. The explanation is that phosphorized-fat when treated with potassium bichromate loses its power of reducing osmic acid; neutral fats are not thus changed. This reaction is not seen in the fat of the cryptorchid testicle.

105 (515)

Studies on experimental arterial lesions in the dog.

By ISAAC LEVIN and JOHN H. LARKIN.

[*From the Department of Pathology, College of Physicians and Surgeons, Columbia University.*]

While it is easy to produce experimentally an arterial lesion in the rabbit, it is extremely difficult to repeat the same in the dog. All attempts to produce arterial lesions in normal dogs, by injection of adrenalin or other similar substances, failed. Carrel and Guthrie, Stich and others stated that the walls of a segment of a vein implanted in an artery undergo certain changes which consist in a hyperplasia of the connective tissue of interstitia, and in an increase of the number of the muscular and elastic fibers of the media. But it is hardly possible to draw a correct conclusion from this method of experimentation, since such a segment is completely severed from its vascular and nerve connections.

Since the majority of writers on arteriosclerosis maintain that the mechanical increase of blood pressure is the most important factor in the causation of the disease, we endeavored in our experiments to increase the blood pressure within the lumen of a vein by the following method:

An anastomosis was performed between the central end of a carotid and the peripheral end of the external jugular vein, thus not only reserving the venous circulation within the blood vessel, but also adding to it the pressure of the arterial blood flowing from the artery.

A certain number of dogs received also from three to five intravenous injections of adrenalin, in order to investigate whether the drug would have any effect on a vein which was already placed under unfavorable conditions of pressure. As a result of the operation there took place in a certain number of cases a dilatation of the external jugular and its branches, with a slight thickening of the vessel wall. In other dogs there took place dilatation of the vein for a distance of about half an inch, where the walls of the blood vessel seemed to arrest the dilatation. Microscopically there was neither degeneration nor hyperplasia of the intima or

media, with the exception of the place near the suture line. Here there was noticeable a hyperplasia of the intima, which was apparently due to the irritation caused by the silk suture acting as a foreign body.

The most important abnormity found in nearly every vessel examined was a new fibrous tissue formation in the adventitia, and this adventitial connective tissue formation was apparently the only cause for the thickening of the wall of the vein on gross inspection.

On the other hand, it is interesting to note that an obliterative endarteritis was found in two experiments where infection took place after the operation.

The conclusion must be drawn, as a result of the investigation, that an arterial lesion cannot be induced artifically on a previously healthy blood vessel of a dog by mechanical change within the vessel.

106 (516)

The relation of the thalamus to respiration, blood pressure and blood supply of the spleen.

By **E. Sachs.** (By invitation.)

[*From the Laboratory of Physiological Chemistry of Cornell University, New York.*]

In the past year I have been carrying on, in Dr. Wolf's laboratory at Cornell, some experiments on the optic thalamus in cats with Clarke's stereotaxic instrument. In some work on the anatomy and physiology of this region, published in *Brain* about a year ago, I showed that the thalamus could be anatomically divided into a median and lateral portion. The lateral was connected with the pre- and post-central gyri, or what corresponds to this area in the carnivora, while the median portion composed of the anterior and median nuclei was intimately connected with the nucleus caudatus and rhinencephalon.

In my present work the relation of the thalamus to blood pressure, respiration and changes in spleen volume was studied. Bechterev and his pupils, Christiani and Ott, have found variations in these functions, and the former has claimed that special centers exist in the thalamus for these functions.

My experiments up to the present time have shown that marked rise in blood pressure occurred on stimulating Meynert's reflex bundle, the median nucleus, the fornix and the anterior commissure. This rise has been, with but one exception, accompanied by a slowing of respiration or apnœa. The lateral part of the thalamus yielded slight, if any, changes in blood pressure.

Changes in spleen volume, with but two exceptions, have never occurred independently of changes in blood pressure. Usually the spleen volume was increased when the blood pressure rose, though on several occasions it fell.

In the anterior corpus quadrigeminum I have several times obtained changes in respiration without changes in blood pressure.

These facts bring out two important points. First of all, that the marked blood pressure changes occur particularly when stimulating the median portion of the thalamus, particularly the olfactory system, somewhere in its course, and as this is highly developed in the Carnivora, it seems most probable that we are dealing here with phenomena following the introduction of strong sensory stimuli rather than independent centers.

Secondly, what is the primary factor in these changes? Are the changes in blood pressure and in spleen volume secondary to respiratory changes or are they phenomena occurring at the same time as, but independent of, the respiratory change? On this point further work is necessary before a positive opinion can be expressed.

107 (517)

The influence of oils and of lecithin on the protein metabolism.

By LLOYD H. MILLS and JOHN R. MURLIN.

[*From the Physiological Laboratory of Cornell University Medical College.*]

Experiments intended to determine the influence of different quantities of vegetable oils, like olive oil, cotton-seed oil, and peanut oil, on the metabolic processes, when injected subcutaneously, have been performed on dogs and rabbits. One experiment on an otherwise fasting dog is presented herewith. The oil given in this case was cotton-seed oil put into the form of a very fine

emulsion in 0.8 per cent. sodium chloride with 5 per cent. lecithin as emulsifier. The dog was kept in the Voit-Pettenkoffer respiration apparatus for about twenty-three hours out of the twenty-

Date.	Food, etc.	Weight.	N in urine + 0.1 gm. for feces. gm.	C of respiration. gm.	Total calories.	Calories per kilo.
March 30	5th day fasting.	9.89	3.15	34.28	401.3	40.5
March 31	80 c.c. emulsion (52 gm. oil) injected subcutaneously.	9.84	3.29	40.50	484.3	49.2
April 1	Fasting.	9.82	2.87	36.02	420.5	42.8
April 2	80 c.c. emulsion taken per os voluntarily.	9.73	3.18	41.78	489.6	50.3

four, and the total metabolism was calculated from the total output of nitrogen and carbon. The dog developed a small abscess from one of the points of injection but there was no fever up to the time the experiment closed, hence we believe the figures given represent a true comparison between the effect of fat fed subcutaneously and the same quantity of the same fat given by mouth. On both food days it will be observed that the total energy production is higher than it is on the fasting days. What is more significant, perhaps, is the fact that this effect of the food to increase the metabolism (specific dynamic action) is relatively greater on the day when the fat was injected subcutaneously than when it was taken in the natural manner. The amount of the oil fed was about sufficient to cover the entire energy requirement of the dog and apparently it was all absorbed from the points of injection (axillæ and groins) into the circulation as completely as it was when absorbed through the alimentary canal.

The nitrogen output was only slightly higher on the day of subcutaneous feeding than on the day of natural feeding. Two other experiments on dogs, one fasting and the other on a standard diet, show the same point. On rabbits otherwise fasting we have found that the effect of oil given subcutaneously, up to 25 per cent. of the calculated requirement, is not distinctly unfavorable in this respect, but does not exert the sparing effect which is noted when an isodynamic quantity of dextrose is given by mouth.

Several experiments with pure lecithin solution indicate that the quantity which can be given to fasting rabbits without un-

favorable effects on the protein metabolism is less than .5 gram per kilogram.

108 (518)

Inheritance of plumage color in poultry.

By **C. B. DAVENPORT.**

[*From the Carnegie Institution of Washington, Station for Experimental Evolution.*]

The experiments of Dr. C. C. Guthrie who transplanted hens' ovaries to foster mothers of different plumage color from their own and was led to the conclusion that the engrafted ovaries became functional and their eggs gained certain characteristics from the foster mothers' are not at all convincing to the student of normal heredity of plumage color in poultry; indeed, they justify the opposite conclusions. To test these experiments, I transplanted ovaries from a cinnamon-colored, heavy-boot, pea-combed, four-toed, low-nostriled hen which breeds true to a white, non-boot, V-combed, five-toed, high-nostriled hen, and mated her with a cock whose characters resembled those of the hen from which the eggs had been borrowed. Had the engrafted ovary been functional, the chicks must all have been like the cock. Actually, they were exactly what expectation calls for when such a cock is mated to a hen like the so-called foster-mother. The engrafted eggs are not functional; the ovary had regenerated.

Six experiments of this sort were made altogether and in no case was there evidence of a functional graft; far less of an influence on the eggs of the foster mother's soma.

109 (519)

A new and comparatively rapid method for the detection of liquefying bacteria.

By **JOHN C. TORREY.**

[*From the Department of Experimental Pathology, Cornell University Medical School.*]

The results obtained by Feldstein and Weil[1] with Ostwald's viscosimeter in an investigation of the interaction of ferment and

[1]*Proc. of the Soc. for Exper. Biol. and Med.*, 1910, vii, 61.

anti-ferment suggested to the writer that this apparatus might be of service for the early detection of the liquefying propensities of those bacteria, which under the methods commonly employed, may not reveal this function for one to four weeks. The identification of *Bacillus coli* in the bacteriological examination of water requires several tests, all of which may be completed within four days, with the exception of that for the action of the bacillus in question on gelatin which calls for a fourteen-day incubation at 20° C. It is generally agreed, among sanitarians, that a shortening of the period of this test is highly desirable, but, although a number of expedients have been suggested, none have been found sufficiently simple and reliable to warrant adoption.

Two special advantages pertain to the use of the viscosimeter in the study of bacterial digestion of gelatin. First, it permits incubation of the cultures at the most favorable temperature, whether it may be 37° C., or higher, thus obtaining rapid growth and enzyme production, although it should be added that these activities are not always correlated; and second, it enables one to detect very slight reductions in the viscosity of the medium, in fact long before any visual change is apparent. It has been found, that, although the majority of cultures, growing well at 37° C., and showing the first evidence of liquefaction at room temperature within three to ten days, may be detected by this method within twenty-four hours, it is best to make the examination after forty-eight hours. After this incubation practically all of the actively growing cultures, which required up to fourteen days for the production of the first visual traces of liquefying activity at 20° C., had produced sufficient change in the viscosity to permit detection. For the still slower liquefiers, those ordinarily requiring a three to four weeks test at 20° C., and for the cultures which grow sluggishly, an incubation of four to six days is necessary for the unquestioned revelation of their fluidifying propensities.

The details in regard to the methods employed and the results obtained will be given elsewhere. Briefly, fifteen per cent. nutrient peptone gelatin, tubed in 4 cubic centimeter amounts, was seeded with a definite dosage of twenty-four-hour agar growth of the culture, emulsified in salt solution. These seeded tubes to-

gether with suitable controls, were then sealed with paraffin and incubated at 36° C. In testing for liquefaction, each gelatin culture and also the control tube were diluted with an equal amount of distilled water and filtered through paper. A viscosimeter tube was selected of sufficient caliber so that the control diluted gelatin passed through in about four minutes. With this control time as a basis, the degree of change Induced in the gelatin by the cultures under consideration could be readily and accurately determined.

110 (520)

On the nature of chemical stimulation and on the influence of neutral sodium salts on various forms of chemical stimulation.

By **RALPH S. LILLIE.**

[*From the University of Pennsylvania.*]

Evidence from many sides indicates that the primary change in the stimulation of an irritable tissue is a sudden increase in the permeability of the boundary layers or "plasma-membranes" of the constituent cells or elements The resistance to the escape of diffusible substances, including carbon dioxide, is thus diminished, and there results a corresponding acceleration of the energy-yielding oxidations. With increase in the permeability to ions, there is naturally also associated a change in the electrical polarization of the plasma-membrane—hence the characteristic "action-current" of stimulation. The primary and critical change, increase of surface permeability, may be produced by the electric current, by sudden changes of temperature or contact, by mechanical shock, or by the action of various chemical substances.

Chemical stimulation, on this view, results from the action of those substances which affect the constituents of the plasma-membrane in such a manner as suddenly to increase its permeability to the critical degree required. Now the plasma-membrane is primarily a colloidal structure, consisting mainly of prothins and lipoids intimately intermixed, possibly intercombined. We should, therefore, expect its structure or consistency to be altered, and its permeability correspondingly increased or decreased, by sub-

stances that influence colloidal aggregation-state; such substances ought, as a class, to show evident relations to stimulation. Again, substances with a specific action on lipoids should also show such relations. These two classes of substances, electrolytes and lipoid-solvents, do in fact show peculiar relations to the stimulation-process; their solutions affect the irritable tissue in two distinct ways; either (1) they stimulate, or (2) without stimulating directly they facilitate or hinder stimulation by other means — in other words, they *sensitize* or *desensitize* the tissue. This means, in terms of the present hypothesis, that such substances either (1) produce rapid increase in the permeability of the plasma-membrance, or (2) alter the readiness with which this change is produced by other means increasing on the one hand (sensitization), or decreasing on the other (desensitization), the liability to such sudden increase of permeability.

In normal or electrical stimulation the increase of permeability is completely and readily reversible, the tissue returning immediately to the resting state on cessation of the stimulus. In contrast to such a condition, many forms of chemical stimulation are found to be imperfectly reversible or, in some cases, completely irreversible. A distinction must, therefore, be made between *reversible* and *irreversible* chemical stimulation. This distinction is illustrated, in the case of frog's skeletal muscle, by the following classification:

A.	Reversible chemical stimulation.	Stimulation by isotonic solutions of neutral sodium salts, and by various other solutions of neutral salts of alkali metals (solutions producing spontaneous twitching).
B.	Irreversible chemical stimulation.	1. Stimulation by solutions of salts of heavy metals, strong acid or alkali, ammonia, etc. 2. Stimulation by concentrated solutions of lipoid-solvents (as chloroform). 3. Stimulation by hemolytics (as saponin), or similarly acting substances (including certain bacterial toxins, as tetanolysin).

In the solutions of Class A, the muscle typically exhibits rhythmical and often energetic twitching, *i. e.*, alternation of contraction and relaxation, and in some cases increase of tone; on return to Ringer's solution, relaxation follows promptly; the normal properties of the tissue remain essentially unaltered. In the solutions of Class B, the contraction is typically slow and steady without twitching, and the contracted state, once attained, persists

after return to the indifferent medium; loss of irritability accompanies the contraction, which is also associated with a coagulation indistinguishable from that of death rigor. In spite of the external differences between the two types of contraction, there is evidence that their fundamental conditions are identical, and that the irreversibility of the second type *depends simply on the irreversibility of the change in the plasma-membrane.* The latter loses its vital semi-permeability *temporarily* in the first, and *permanently* in the second case; the loss of irritability and the coincident rigor or contracture are consequences of this permanent loss of the normal condition of semi-permeability.

The distinction between reversibility and irreversibility in the stimulating action of salts undoubtedly has as its ground the similar distinction in the action of salts on the aggregation-state of proteins. Alkali and alkali-earth neutral salts produce reversible changes in the colloidal aggregation-state, while with heavy metal salts the aggregation-changes are irreversible (*Pauli*). In correspondence with this difference, it is found that the stimulating (or inhibiting) effects produced by the first group of salts are reversible, while those produced by the second are irreversible. In the case of lipoid-solvents in strong solution (which also produce contracture passing into rigor) it is to be assumed that the lipoids in the plasma-membrane undergo a change of state too far-reaching to be reversible (dissolving out, etc.). Hemolytics and other poisons must be assumed to act by virtue of various special peculiarities; thus saponin, *e. g.*, probably alters the condition of the cholesterin and so destroys the semi-permeability of the membrane.

In the following experiments the sensitizing and desensitizing action of various electrolytes has been studied in relation to the above different forms of chemical stimulation. Frog's gastrocnemii have been chiefly used. The muscle, arranged to write on a drum, is brought from Ringer's solution into the stimulating solution (where it contracts, describing a curve); after a definite interval (1 to 2 minutes) it is returned to Ringer; relaxation may or may not follow, according to the character of the stimulus. The same muscle (if reversible stimulation is used), or the other muscle of the same animal (with irreversible stimulation), is then exposed

for a definite period to the sensitizing (or desensitizing) solution, *e. g.*, is placed for four minutes in *m*/8 NaBr, from which it is transferred directly to the stimulating solution; the response, if sensitization has occurred, is found to be more energetic than before; if desensitization has occurred, it is lessened or abolished.

The relative sensitizing powers of a series of sodium salts have been thus determined, using the following solutions as stimuli:

1. *m*/8 KCl.

2. Isotonic solutions of sodium salts containing potassium (to increase the twitching effect), *e. g.*, 7 vols. *m*/8 NaI + 1 vol. *m*/8 KI.

3. Pure isotonic solutions of sodium salts which produce active twitching: acetate, sulphate, tartrate, citrate.

4. Saturated solution of a typical lipoid solvent, chloroform, in Ringer's solution.

5. Solution of a typical hemolytic, 0.2 per cent. saponin, in Ringer's solution.

All of these solutions produce contraction in fresh normal muscle. The response is typically and often markedly increased after treatment with pure solutions of sodium salts, especially sodium nitrate, sodium chlorate, sodium sulpho-cyanate and sodium iodide. Magnesium and calcium chlorides, on the other hand, decrease the response *to all salts*, but not to chloroform or saponin. A difference thus appears according to whether the stimulating solution has a general action on colloids, or affects primarily the lipoids.

The order of relative sensitizing action for isotonic solutions of the following sodium salts is, in general, as follows: $NaCl < NaBr < NaNO_3 < NaClO_3 < NaI$ and NaCNS. This statement applies more particularly to stimuli (1), (2), (4) and (5); the salts in group (3), especially sulphate, tartrate and citrate (which appear to act by lowering the concentration of Ca-ions) show somewhat different relations. The above order corresponds to the order of relative action on colloids, and indicates that the salts increase irritability by altering, *in the direction of increased dispersion*, the state of subdivision of the colloidal constituents of the plasma-membrane. The desensitizing or anesthetic action of the alkali-earth chlorides is presumably dependent on an alteration of the plasma-membrane colloids in the reverse direction.

The response of a muscle to chloroform or saponin after treatment with a strongly sensitizing solution, as $m/8$ NaI, $m/8$ $NaClO_3$, $m/8$ $NaNO_3$, or $m/8$ NaCNS, approaches closely in character to the normal contraction, *i. e.*, the upstroke is rapid and accompanied by often vigorous twitching. There is, however, *no relaxation;* and the associated coagulative change in the tissue-colloids is more pronounced than in the unsensitized muscle similarly treated. In other words, *there is a correlation between the vigor of the contraction and the degree of the coagulation*, indicating that the fundamental change in contraction is of the same nature as in colloid coagulation, *i. e.*, that contraction is the expression of a coalescence of colloidal particles in the fibrillæ, due presumably to increased surface-tension of these particles. These experiments also indicate that rigor contraction is of the same essential nature as normal contraction.

111 (521)

A new method for the analysis of proteins.

By **DONALD D. VAN SLYKE.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

The method outlined will serve to supplement the ester method, and to characterize proteins when relatively small amounts of material are available. Two and a half grams of protein are hydrolyzed by 15 to 18 hours boiling with 20 per cent. hydrochloric acid. The solution is concentrated to a syrup, then transferred to a one-liter Claissen distilling flask with 200 cubic centimeters of water. Saturated barium hydrate solution to 25 cubic centimeters excess is added and the *ammonia* is distilled *in vacuo* into $N/10$ sulphuric acid from a bath at 45° C. The residual solution is acidified with sulphuric acid and boiled while silver sulphate is added until all the hydrochloric acid is precipitated. The precipitate, which carries the *melanine* with it, is Kjeldahled to determine the melanine nitrogen. The filtrate is brought to 100 cubic centimeters and 5 cubic centimeter duplicates taken for total and amino nitrogen determinations.[1]

[1]Method for Determination of Amino Nitrogen, *Proc. of the Soc. for Exper. Biol. and Med.*, 1909, vii, 46.

The remaining 80 cubic centimeters are precipitated with phosphotungstic acid as described by Osborne and Harris,[2] except that twice the volume of solution is employed and the bases are given forty-eight hours to precipitate. It has been found that cystine is precipitated quantitatively with the hexone bases. The phosphotungstates are washed with suction, and decomposed in the cold with a slight excess of barium hydrate solution. The excess barium is precipitated as carbonate. The solution is then concentrated at a low temperature and brought to 50 cubic centimeters; 10 cubic centimeter samples are taken for total and amino nitrogen determinations. The remaining 30 cubic centimeters are washed in a copper Kjeldahl flask with 20 cubic centimeters of water and 15 grams of solid reagent sodium hydrate. The mixture is boiled six hours under a reflux condenser, the top of which is closed by a Folin 3-bulb tube containing 20 cubic centimeters of $N/10$ sulphuric acid. One-half the *arginine* is split off as ammonia,[3] the reaction being quantitative under the conditions here outlined. 90 to 98 per cent. of the ammonia is caught and titrated in the acid of the Folin tube. The remaining 2 to 10 per cent. is boiled off on a Kjeldahl still, after the alkaline solution has been diluted. The bases, other than arginine, give off no ammonia. To the solution used for arginine determination one adds 3 grams of potassium nitrate, concentrates, fuses and determines the sulphur, from which the *cystine* is calculated. By these determinations the phosphotungstate precipitate is divided as follows:

- Phosphotungstate precipitate
  - Non-amino N
    - *Arginine* (¾ of nitrogen, non-amino), determined by decomposing with sodium hydroxide.
    - *Histidine* (⅔ of nitrogen, non-amino) by difference from the arginine.
  - Amino N
    - *Cystine* (all of nitrogen, amino), determined by sulphur.
    - *Lysine* (all of nitrogen, amino), by difference from cystine.

The amino and non-amino nitrogen in the phosphotungstic filtrate are determined by difference, avoiding the necessity of Kjeldahling solutions containing phosphotungstic acid. The filtrate is freed from phosphotungstic and sulphuric acids with

[2] *Jour. of the Amer. Chem. Soc.*, 1903, xxv, 323.

[3] Osborne, Leavenworth, and Brautlecht, *American Jour. of Physiol.*, 1908, xxiii, 180.

barium hydrate, from barium hydrate with carbon dioxide, and at the end, an *exact* equivalent of sulphuric acid. This leaves only the mono-amino acids in solution. It has been found that all the known acids of this class react neutrally to indicators changing color at $H^+ = 10^{-7}$, except the dicarboxylic acids, glutaminic and aspartic, and these can be titrated accurately as monobasic acids, even in the presence of the others, with rosalic acid as indicator. The amino acids not precipitated by phosphotungstic are, therefore, divided as follows:

Phosphotungstate filtrate { Non-amino nitrogen, *prolin, oxyprolin, ½ tryptophane,* and possibly unknown acids. / Amino nitrogen { *Dicarboxylic acids (glutaminic and aspartic).* / *Mono-carboxylic acids (leucin, alanin, etc.).*

The method is being applied, among other things, to a study of the fibrinoses in progress with Drs. Levene and Birchard in this laboratory.

112 (522)

The determination of amino nitrogen as a measure of the rate and extent of proteolysis.

By **DONALD D. VAN SLYKE.**

[*From the Laboratories of the Rockefeller Institute for Medical Research.*]

Amino acids in proteins, as shown by Emil Fischer's work, are undoubtedly bound together by peptid (-CO-NH-) linkings, the nitrogen in these linkings being in the *imino* form. When hydrolysis occurs, the peptid linkings are split, yielding -COOH and $-NH_2$ derivations. The hydrolysis of each peptid linking, therefore, frees an *amino* group. Consequently, determination of the amino nitrogen should afford direct chemical measure of the rate and extent to which a protein is hydrolyzed, whether by action of acids, alkalies or enzymes. It should also indicate the relative molecular size of isolated intermediate products, such as albumoses, peptones and peptids, as the larger molecules have relatively more nitrogen in the peptide linkings, and less amino nitrogen. Results have been obtained which indicate that the amino determination fulfills the above requirements of the theory of protein structure, and that it will be of practical value in the study of enzyme action and of the products of partial hydrolysis.

It has been found that every known amino acid obtained by proteolysis, except prolin and oxyprolin, gives off one or more atoms of nitrogen when treated with nitrous acid.[1] The dipeptids, leucyl-leucin and leucyl-glycin, give off to nitrous acid only one atom of nitrogen each, the atom in the peptid linking not being removed. Glycin anhydride, containing two atoms of nitrogen, both in peptid form, gives off no nitrogen at all. Peptides having serin or glycin on the end of the chain containing the free amino group may yield somewhat more than the theoretical one atom of nitrogen, for reasons which will be shown later. With the exception of such peptides, which cannot be yielded by most proteins in sufficient amount to interfere appreciably with determinations, agreement between theory and results appears absolute. Native proteins show but minimal amounts of amino nitrogen. The proportion is greater in the primary albumoses, and still greater in the deutero. (The albumose results will be published shortly with Drs. Levene and Birchard.) The progressive increase of amino nitrogen during hydrolysis is shown by the following series: egg albumen in 2 per cent. solution was submitted to the action of 5 per cent. sodium hydrate at 60°, 5 cubic centimeter samples being drawn at intervals for amino determination. Addition of an occasional drop of amyl alcohol during the earlier determinations is necessary to prevent foaming of the viscous solutions.

Time in hours.	Per cent. of nitrogen in amino form.
0	3.0
0.5	7.15
1.5	10.31
4.5	19.45
12.0	28.22
24.0	39.02
48.0	46.62
72.0	54.02
96.0	61.10
144.0	68.42

Completely hydrolized albumen contains 8.5 per cent. of its nitrogen in amino form.

A similar, but much more rapid increase was obtained when

[1] *Proc. of the Soc. for Exper. Biol. and Med.*, 1909, vii, 46. The apparatus in improved form is manufactured by Machlett & Sons, New York.

casein was heated at 80° with 20 per cent. hydrochloric acid. In this case, hydrolysis was complete in ten hours, the amino nitrogen having reached its maximum, 71 per cent. of the total.

113 (523)

A demonstration of Krogh's micro-tonometer for the determination of gas tensions in fluids.

By **M. M. SCARBROUGH.** (By invitation.)

[*From the Physiological Laboratory, Department of Medicine, Yale University.*]

The advantages of Krogh's apparatus are, first, the small amount of fluid required; second, the large specific surface obtained; third, the rapidity and accuracy of determinations. The bubble of gas used is about 2 mm. in diameter, having a specific surface of 30 as compared with a specific surface of 3.3 in Pflüger's aërotonometer, 5.2 in Bohr's hemataërometer and 3.7 in Fredericq's. A fine spray of the fluid to be examined is played on the bubble for a few minutes; the bubble is then drawn into a capillary burette where it is measured before and after the absorption of oxygen and carbon dioxide. For carbon dioxide alone in fluids, a very simple vessel is used; the tonometry is accomplished by shaking a small bubble of air with a relatively large amount of fluid. The bubble is then transferred to the capillary burette and analyzed. The limit of error can be brought down to + 0.2 per cent.[1]

114 (524)

Breeding experiments in poultry.

By **H. D. GOODALE.** (By invitation.)

A. *Note on the Results of a White Leghorn by White Plymouth Rock Cross.*

The cross was made in only one way, viz., white Leghorn females × White Plymouth Rock males. The chicks were white with sometimes a few black spots. They developed into white birds, with a few black spots. Later the surface color became

[1]For full description of apparatus and methods see Krogh's articles in *Skandinavisches Archiv für Physiologie*, 1908, xx, 259–288.

dulled owing to the development of minute spots of pigment. At the same time, faint bars developed in some birds though they were wanting in others. F_2 contains white, black, gray and barred chicks, the last exactly like those of Barred Plymouth Rocks.

B. *Peculiarities in Inheritance of Brown Leghorn Color in Relation to Sex.*

Experiment I.—Brown Leghorn females × White Plymouth Rock males gave both sexes barred. The males are splashed with Brown Leghorn color, which is lacking in the females.

Experiment II.—White Plymouth Rock females × Brown Leghorn males gave barred males like those of Experiment I. The females are either nearly black with orange hackle or else approach fairly closely the color of a Brown Leghorn female. The White Plymouth Rock females appear then to be heterozygous for barring, and the Brown Leghorn females for some factor for color or pattern.

Experiment III.—F_1, females from Experiment I, bred to their father gave 27 white and 26 barred chicks. Even the males that were reared showed no trace of Brown Leghorn color.

Experiment IV.—White Plymouth Rock females × a male from Experiment I thus far have given 1 black, 14 white, 6 barred, 2 Brown Leghorn.

Experiment V.—F_1, females (Experiment I) × brown Leghorn male has given 12 barred, 5 black, 11 Leghorn, 4 modified Leghorn.

Experiment VI.—F_1, females (Experiment I) × White Langshan male (gametic constitution unknown) is giving black, white, barred and red chicks. The reds probably come from the father.

Experiment VII.—F_2, barred females (Experiment III) × White Langshan male is giving white, black and barred chicks.

Experiment VIII.—F_2, white females (Experiment III) × White Langshan male is giving only whites.

Experiment IX.—F_1, females (Experiment II) × White Langshan is giving white, black and reddish chicks.

Experiment X.—F_1, females (Experiment II) × White Rock is giving barred and white chicks.

Since Experiment III produced no Brown Leghorn chicks and since such occurred in Experiment IV, we are justified in believing that the Brown Leghorn color exists in a heterozygous condition in the female but not in the male, thus confirming Bateson's theory of sex. As this color pattern is nearly, if not quite identical with that of *Gallus bankiva*, it will be interesting to know if the heterozygous condition is common to all the domestic races of poultry bearing this ancestral color. Hagedoorn has described such a case, but also describes the reverse, *i. e.*, heterozygous males and homozygous females.

115 (525)

Inflammation in tissues separated from connection with the central nervous system.

By **W. G. MACCALLUM, M.D.**

[*From the Department of Pathology, College of Physicians and Surgeons Columbia University.*]

An attempt was made to study the cause of inflammation in tissues separated from connection with the central nervous system as compared with that in normal tissues. The mere section of the nerves going to an organ or limb is insufficient, for nerve fibrils accompany the blood vessels. To overcome this an extremity was amputated completely and replaced by anastomosing the blood vessels and bringing together muscles and skin. Inflammatory irritants applied symmetrically to the intact, and to the amputated limb of the dog resulted in the production of quite the same phenomena of inflammation on both sides. The reddening due to the dilatation of the blood vessels was perhaps slightly more intense on the amputated side than in the intact limb. Evidently, the control of the central nervous system is not at all necessary for the development of inflammatory changes.

RECAPITULATION OF THE NAMES OF THE AUTHORS AND OF THE TITLES OF THE COMMUNICATIONS.

VOLUME VII.

Anderson, John F.

431. [with **W. H. Schultz.**] The cause of serum anaphylactic shock and some methods of alleviating it.

461. [with **Joseph Goldberger.**] A report on the production of tabardillo, or Mexican typhus fever, in monkeys.

Atkinson, J. P.

455. [with **C. B. Fitzpatrick.**] Notes on sensitization with tuberculin to tubercular rabbit-serum.

475. [with **C. B. Fitzpatrick.**] Notes on the vaso reaction in dogs produced by injections of extracts of the tubercle bacillus.

503. [with **C. B. Fitzpatrick.**] Vaso-response in dogs to hydrophobia rabbit serum.

504. [with **Edwin J. Banzhaf.**] On the precipitation of diphtheria antitoxin by precipitins.

Auer, J.

426. [with **S. J. Meltzer.**] Respiration by continuous intra-tracheal insufflation of air. A demonstration.

429. [with **P. A. Lewis.**] A demonstration of the cause of acute anaphylactic death in guinea pigs.

474. The effects of resection of one vagus upon serum anaphylaxis in guinea-pigs.

Banzhaf, Edwin J.

454. [with **Edna Steinhardt.**] Vaughan's split products and unbroken proteins. A comparative study of their effects.

504. [with **J. P. Atkinson.**] On the precipitation of diphtheria antitoxin by precipitins.

Barker, Bertha I. [with **Eugene L. Opie.**]

472. Enzymes and antienzymes of the blood serum with certain degenerative changes in the liver.

Benson, Robert L. [with **H. Gideon Wells.**]

414. The study of autolysis by physico-chemical methods.

Burton-Opitz, R.

450. On the vaso-motor nerves of the stomach.

451. [with **H. F. Wolf.**] The change in the venous blood-flow on administration of amyl nitrite.

Carlson, A. J.

442. [with **Clara Jacobson.**] The depression of the ammonia destroying power of the liver after thyroid-parathyroidectomy.

443. [with **A. L. Crittenden.**] The relation of ptyalin concentration to the diet and to the rate of salivary secretion.

Carpenter, Thorne M. [with **John R. Murlin.**]

442. The energy metabolism of parturient women.

Carrel, Alexis.

427. Demonstration of animals whose thoracic organs have been operated upon.

456. Remote results of the replantation of the kidneys.

457. Temporary diversion from the left ventricle to the descending aorta.

Cooke, Jean V. (By invitation.)

419. The excretion of calcium and magnesium after parathyroidectomy.

Crile, George W.

462. On the neurocytologic changes in shock, infection, Graves' disease, and certain drugs, with a note on fear in rabbits.

463. Further observations on hemolysis in cancer.

464. On the behavior of autodermic and isodermic skin grafts in cancer.

Crittenden, A. L. [with **A. J. Carlson.**]

443. The relation of ptyalin concentration to the diet and to the rate of salivary secretion.

Davenport, Charles B.

518. Inheritance of plumage color in poultry.

Dochez, A. R.

471. Intracellular proteolytic enzymes of liver.

491. The activation of pancreatic extract.

Eisenbrey, Arthur Bradley.

430. [with **Richard M. Pearce.**] Anaphylactic "shock" in the dog.

459. [with **Richard M. Pearce.**] The mechanism of the depressor action of dog's urine with some observations on the antagonistic action of adrenalin.

482. A method of isolating the cerebro-medullary circulation.

Emery, W. O. [with **W. Salant.**]

509. The elimination of caffein in the bile.

Feldstein, S. [with **R. Weil.**]

447. A new method for testing the interaction of ferments and anti-ferments.

500. Observations on the nature of the antitrypsin of the serum.

Fitzpatrick, C. B. [with **J. P. Atkinson.**]

455. Notes on sensitization with tuberculin to tubercular rabbit-serum.

475. Notes on the vaso reaction in dogs produced by injections of extracts of the tubercle bacillus.

503. Vaso-response in dogs to hydrophobia rabbit serum.

Fleisher, Moyer S. [with **Leo Loeb.**]

467. The adsorption of the venom of *Heloderma suspectum.*

Flexner, Simon. [with **Paul A. Lewis.**]

441. A report on experimental poliomyelitis.

Foster, N. B.

480. Nitrogen and sulphur metabolism in morbus cruleus.

Gay, Frederick P. [with **William P. Lucas.**]

424. The value of the conglutination reaction as a means of diagnosis of acute bacterial infections.

Goldberger, Joseph. [with **John F. Anderson.**]

461. A report on the production of tabardillo, or Mexican typhus fever, in monkeys.

Goodale, H. P. (By invitation.)

524. Breeding experiments in poultry.

Guthrie, C. C.

434. [with **A. H. Ryan** and **F. V. Guthrie.**] The action of magnesium salts: (A) In relation to motor nerve impulses; (B) In relation to sensory stimulation.

435. [with **A. H. Ryan** and **F. V. Guthrie.**] The effects of direct application of magnesium salts: (A) To motor and sensory nerves; (B) To cardio-inhibitory nerves.

436. The survival and growth of subcutaneously engrafted ovarian and testicular tissue.

437. The survival of engrafted thyroid and renal tissue.

438. The effect of anemia and of double hyperemia on hyperplastic goitre.

505. Further observations on the structure of anastomosed blood vessels.

Guthrie, F. V.

434. [with **A. H. Ryan** and **C. C. Guthrie.**] The action of magnesium salts: (A) In relation to motor nerve impulses; (B) In relation to sensory stimulation.

435. [with **A. H. Ryan** and **C. C. Guthrie.**] The effects of direct application of magnesium salts: (A) To motor and sensory nerves; (B) To cardio-inhibitory nerves.

506. (By invitation.) Modification of tissue oxidations *in vitro.*

Hanes, F. M. (By invitation.)

514. The biological significance of the Sertoli cells.

Harvey, E. N. [with **Frederic S. Lee.**]

494. An examination of Fröhlich's theory of the treppe.

Henderson, Yandell.

499. The fundamental conditions of surgical shock.

Hess, Alfred F.

460. On the elimination of bacteria from the blood through the wall of the intestine.

Hooker, Davenport. (By invitation.)

507. The development and function of the heart in embryos without nerves.

Hunter, Andrew.

416. A method for the determination of small quantities of iodine in organic material.

417. [with **Sutherland Simpson.**] Relations between the thyroid and pituitary glands.

Jacobs, W. A. [with **P. A. Levene.**]

465. On yeast nucleic acid.

Jacobson, Clara.

442. [with **A. J. Carlson.**] The depression of the ammonia destroying power of the liver after thryoid-parathyroidectomy.

487. (By invitation.) The concentration of ammonia in the blood of dogs and cats necessary to produce ammonia tetany.

Janeway, Theodore C. [with **Edwards A. Park.**]

510. An experimental study of the resistance to compression of the arterial wall.

Joseph, Don R. [with **S. J. Meltzer.**]

428. The mutual antagonistic life-saving action of barium and magnesium. A demonstration.

449. The inhibitory effect of magnesium upon indirect and direct irritability of frog muscle and the antagonistic action of sodium and calcium upon this effect.

469. A demonstration of the inhibitory effect of magnesium upon normal and artificial peristalsis of the stomach and duodenum.

Kast, L.

432. The influence of glycerin on gastric secretion.

Koch, W. [with **F. W. Upson.**]

413. The distribution of sulphur compounds in brain tissue.

Lamar, R. V. [with **S. J. Meltzer.**]

473. A preliminary note upon experimental lobar pneumonia with a demonstration of specimens.

Lambert, R. A. (By invitation.)

468. A note on the parabiosis of rats and mice.

Larkin, John H. [with **Isaac Levin.**]

477. The early stages of the spontaneous arterial lesions in the rabbit.

515. Studies on experimental arterial lesions in the dog.

Lee, Frederic S.

433. [with **Max Morse.**] The summation of stimuli.

494. [with **E. N. Harvey.**] An examination of Fröhlich's theory of the treppe.

Levene, P. A.

465. [with **W. A. Jacobs.**] On yeast nucleic acid.

481. [with **G. M. Meyer.**] On parenteral protein assimilation.

Levin, Isaac.

448. Resistance to the growth of cancer induced in rats by injection of autolyzed rat tissue.

476. Immunity to the growth of cancer induced in rats by treatment with mouse tissue.

477. [with **John H. Larkin.**] The early stages of the spontaneous arterial lesions in the rabbit.

515. [with **John H. Larkin.**] Studies on experimental arterial lesions in the dog.

Lewis, P. A.

429. [with **J. Auer.**] A demonstration of the cause of acute anaphylactic death in guinea pigs.

441. [with **Simon Flexner.**] A report on experimental poliomyelitis.

Lillie, Ralph S.

520. On the nature of chemical stimulation and on the influence of neutral sodium salts on various forms of chemical stimulation.

Loeb, Jacques.

484. The rôle of alkali in the development of the egg of the sea-urchin.

485. How can the process underlying membrane formation cause the development of the egg?

Loeb, Leo.

466. The reaction of the uterine mucosa towards foreign bodies introduced into the uterine cavity.

467. [with **Moyer S. Fleisher.**] The adsorption of the venom of *Heloderma suspectum.*

Lucas, William P. [with **Frederick P. Gay.**]

424. The value of the conglutination reaction as a means of diagnosis of acute bacterial infections.

Luckhardt, Arno B.

486. A study of the origin of the immune bodies by the method of organ transplantation.

Lusk, Graham.

495. An attempt to discover the cause of the specific dynamic action of protein.

493. [with **A. I. Ringer.**] The non-production of sugar from tyrosin and glucosamin phlorizin glycosuria.

Lyman, John F. [with **Lafayette B. Mendel.**]

497. The metabolism of the purines in man.

Lyon, E. P. [with **J. L. Swarts.**]

498. The distribution of blood in shock.

MacCallum, W. G.

525. Inflammation in tissues separated from connection with the central nervous system.

McClendon, J. F.

478. Artificial cyclopia in the smelt.

479. Cataphoresis of proteids in the living cell.

Mandel, J. A.

425. Analysis of the cleavage products of the nucleoprotein of the mammary glands.

Mayer, Alfred G.

423. The relation between ciliary and muscular movements.

Meltzer, S. J.

426. [with **J. Auer.**] Respiration by continuous intratracheal insufflation of air. A demonstration.

428. [with **Don R. Joseph.**] The mutual antagonistic life-saving action of barium and magnesium. A demonstration.

449. [with **Don R. Joseph.**] The inhibitory effect of magnesium upon indirect and direct irritability of frog muscle and the antagonistic action of sodium and calcium upon this effect.

469. [with **Don R. Joseph.**] A demonstration of the inhibitory effect of magnesium upon normal and artificial peristalsis of the stomach and duodenum.

470. [with **A. O. Shaklee.**] Recovery from fatal doses

of strychnin by the aid of curarin and artificial respiration (insufflation method).

473. [with **R. V. Lamar.**] A preliminary note upon experimental lobar pneumonia with a demonstration of specimens.

Mendel, Lafayette B. [with **John F. Lyman.**]

497. The metabolism of the purines in man.

Meyer, G. M. [with **P. A. Levene.**]

481. On parenteral protein assimilation.

Mills, Lloyd H. [with **John R. Murlin.**]

517. The influence of oils and of lecithin on the protein metabolism.

Morgan, T. H.

492. Experiments bearing on the nature of the karyokinetic figure.

512. Hybridization in a mutating period in *Drosophila.*

513. The chromosomes in the parthenogenetic and sexual eggs of phylloxerans and aphids.

Morse, Max.

433. [with **Frederic S. Lee.**] The summation of stimuli.

446. Shaking experiments with protozoa.

502. Alleged rhythm in phototaxis synchronous with ocean tides.

Murlin, John R.

422. [with **Thorne M. Carpenter.**] The energy metabolism of parturient women.

488. The daily curve of nitrogen elimination in the pregnant, as compared with the non-pregnant dog.

517. [with **Lloyd H. Mills.**] The influence of oils and of lecithin on the protein metabolism.

Noguchi, Hideyo.

420. Non-fixation of complement.

421. The fate of so-called syphilitic antibody in the precipitin reaction.

444. On non-specific complement fixation.

Opie, Eugene L.

445. Experimental cirrhosis of the liver.

472. [with **Bertha I. Barker.**] Enzymes and antienzymes

of the blood serum with certain degenerative changes in the liver.

Ott, Isaac. [with **John C. Scott.**]

440. Note on the production of glycosuria by parathyroids, pancreas and the infundibular extract of the pituitary.

Park, Edwards A. [with **Theodore C. Janeway.**]

510. An experimental study of the resistance to compression of the arterial wall.

Pearce, Richard M. [with **A. B. Eisenbrey.**]

430. Anaphylactic "shock" in the dog.

459. The mechanism of the depressor action of dog's urine with some observations on the antagonistic action of adrenalin.

Reichert, Edward Tyson.

483. A reversion of the starch-dextrin reaction.

Ringer, A. I.

415. (By invitation.) Influence of adrenalin in phlorizin diabetes.

493. [with **Graham Lusk.**] The non-production of sugar from tyrosin and glucosamin phlorizin glycosuria.

Rose, William C.

493. [with **Graham Lusk.**] The non production of sugar.

496. (By invitation.) Demonstration of a modified method of estimating pepsin.

Rous, Peyton.

418. Parabiosis as a test for circulating antibodies in cancer.

452. The fate of embryonic tissue implanted in the mother.

453. The behavior of transplanted mixtures of tumor and embryo.

Ryan, A. H. [with **F. V.** and **C. C. Guthrie.**]

434. The action of magnesium salts: (A) In relation to motor nerve impulses; (B) In relation to sensory stimulation.

435. The effects of direct application of magnesium salts: (A) To motor and sensory nerves; (B) To cardio-inhibitory nerves.

Sachs, E.

516. (By invitation.) The relation of the thalamus to respiration, blood pressure and blood supply of the spleen.

Salant, William.

508. The toxicity of amyl acetate.

509. [with **W. O. Emery.**] The elimination of caffein in the bile.

Scarbrough, M. M.

523. (By invitation.) A demonstration of Krogh's microtonometer for the determination of gas tensions in fluids.

Schultz, W. H. [with **John F. Anderson.**]

431. The cause of serum anaphylactic shock and some methods of alleviating it.

Scott, John C. [with **Isaac Ott.**]

440. Note on the production of glycosuria by parathyroids, pancreas and the infundibular extract of the pituitary.

Shaklee, A. O.

470. [with **S. J. Meltzer.**] Recovery from fatal doses of strychnin by the aid of curarin and artificial respiration (insufflation method).

511. A simple device for regulating the administration of ether or chlorofrom, with either artificial or voluntary respiration.

Simpson, Sutherland. [with **Andrew Hunter.**]

417. Relations between the thyroid and pituitary glands.

Steinhardt, Edna.

454. [with **Edwin J. Banzhaf.**] Vaughan's split products and unbroken proteins. A comparative study of their effects.

490. Filtration through collodion sacs.

Stockard, Charles R.

411. The influence of alcohol and other anesthetics on developing embryos.

Swarts, J. L. [with **E. P. Lyon.**]

498. The distribution of blood in shock.

Torrey, John C.

519. A new and comparatively rapid method for the detection of liquefying bacteria.

Upson, F. W. [with **W. Koch.**]

413. The distribution of sulphur compounds in brain tissue.

Van Slyke, Donald D.

439. A method for the determination of amino nitrogen and its applications.

521. A new method for the analysis of proteins.

522. The determination of amino nitrogen as a measure of the rate and extent of proteolysis.

Weil, Richard.

412. On the variation in the resistance of human erythrocytes in disease to hemolysins, with especial reference to syphilis.

447. [with **S. Feldstein.**] A new method for testing the interaction of ferments and anti-ferments.

500. [with **S. Feldstein.**] Observations on the nature of the antitrypsin of the serum.

Wells, H. Gideon. [with **Robert L. Benson.**]

414. The study of autolysis by physico-chemical methods.

Williams, Horatio B. (By invitation.)

489. Contraction of muscle during voluntary innervation.

Wolf, H. F. [with **R. Burton-Opitz.**]

451. The change in the venous blood flow on administration of amyl nitrite.

Woodruff, Lorande Loss.

501. On the power of reproduction without conjugation in Paramecium.

EXECUTIVE PROCEEDINGS.

Thirty fifth meeting.

College of Physicians and Surgeons, Columbia University, October 20, 1909. President Lee in the chair.

Members present: Auer, Ewing, Famulener, Foster, Gies, Harris, Hatcher, Hunter, Joseph, Lamar, Lee, Levene, Levin, Meltzer, Mayer, Meyer, Morgan, Morse, Murlin, Norris, Noguchi, Opie, Park, Pearce, Rous, Symmers, Schaffer, Stockard, Van Slyke, Wadsworth, Weil, Wolf, Zinsser.

Thirty sixth meeting.

The Rockefeller Institute for Medical Research, December 15, 1909. President Lee in the chair.

Members present: Atkinson, Auer, Banzhaf, Beebe, Brodie, Cole, Famulener, Gay, Gies, Harris, Jackson, Joseph, Kast, Lamar, Lee, Levene, Levin, Lewis, Lusk, Mandel, Maury, Meltzer, Morgan, Murlin, Moss, Opie, Pearce, Rous, Shaffer, Shaklee, Van Slyke, Wallace, Wolf.

Members elected: Stanley R. Benedict, Alfred F. Hess, A. W. Hewlett, J. F. McClendon, Raymond Pearl, A. I. Ringer, A. O. Shaklee, Sutherland Simpson and Hugh A. Stewart.

Thirty seventh meeting.

New York University and Bellevue Hospital Medical College, February 16, 1910. President Lee in the chair.

Members present: Atkinson, Auer, Banzhaf, Cole, R. I., Flexner, Gies, Hiss, Jackson, Joseph, Lee, Levin, Lusk, Mandel, A. R., MacCallum, McClendon, Meltzer, Morgan, Moss, Opie, Park, Rous, Shaklee, Stockard, Van Slyke, Wallace, Weil.

Members elected: J. V. Cooke, A. R. Dochez, J. B. Leathes.

Officers elected: President, Thomas H. Morgan; Vice-President, William J. Gies; Secretary, Eugene L. Opie; Treasurer, Graham Lusk.

Thirty eighth meeting.

Cornell University Medical College, April 20, 1910. President Morgan in the chair.

Members present: Atkinson, Auer, Beebe, Cole, R. I., Cooke, Crile, Dochez, Ewing, Foster, Gies, Jackson, Jacobs, Joseph, Kast, Lamar, Lee, Levin, Loeb, L., Lusk, MacCallum, McClendon, Meltzer, Meyer, A., Morgan, Murlin, Noguchi, Opie, Pearce, Rous, Shaffer, Shaklee, Torrey, Van Slyke, Weil, Wolf.

Members elected: Herman M. Adler, Katharine R. Collins, A. J. Goldfarb, Anna W. Williams.

Thirty ninth meeting.

Sheffield Biological Laboratory, New Haven, May 18, 1910. President Morgan in the chair.

Members present: Atkinson, Beebe, Davenport, Gies, Harrison, Henderson, Janeway, Lee, Levin, I., Lusk, MacCallum, Meltzer, Mendel, Morgan, Murlin, Norris, Pearce, Shaklee, Stewart, H. A., Wolf.

Members elected: A. B. Eisenbrey, H. D. Senior, Edna Steinhardt, H. F. Swift.

REGISTER OF NAMES AND ADDRESSES OF THE MEMBERS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE.

ABBOTT, ALEXANDER C.....University of Pennsylvania.
ABEL, JOHN J.....Johns Hopkins University.
ADAMI, J. GEORGE.....McGill University, Montreal.
ADLER, HERMAN M.....Danvers Insane Hospital, Hathorne, Mass.
ADLER, ISAAC.....New York Polyclinic Medical School.
ALSBERG, CARL L.....U. S. Department of Agriculture, Washington, D. C.
ANDERSON, JOHN F.....U. S. Public Health and Marine-Hospital Service, Hygienic Laboratory, Washington, D. C.
ATKINSON, JAMES P.....Department of Health, New York City.
AUER, JOHN.....Rockefeller Institute for Medical Research.

BANZHAF, EDWIN J.....Department of Health, New York City.
BARDEEN, CHARLES R.....University of Wisconsin.
BEEBE, SILAS P.....Cornell University Medical College.
BENEDICT, FRANCIS G...Nutrition Laboratory, Carnegie Institution, Boston.
BENEDICT, STANLEY R.....Columbia University.
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BRODIE, T. G.....University of Toronto.
BROOKS, HARLOW.....New York University.
BUNTING, C. H.....University of Wisconsin.
BURTON-OPITZ, RUSSELL.....Columbia University.
BUXTON, B. H.....Cornell University Medical College.

CALKINS, GARY N.....Columbia University.
CANNON, Walter B.....Harvard University.
CARLSON, A. J.....University of Chicago.
CARREL, ALEXIS.....Rockefeller Institute for Medical Research.
CHITTENDEN, R. H.....Yale University.
CLOWES, G. H. A.....University of Buffalo.
COLE, L. J.....Yale University.
COLE, RUFUS I.....Rockefeller Institute for Medical Research.
COLLINS, KATHARINE R.....State Board of Health, Atlanta, Ga.
CONKLIN, EDWIN G.....Princeton University.

Cooke, J. V.....New York University.
Councilman, William T.....Harvard University.
Crampton, C. Ward.....Department of Education, New York City.
Crampton, Henry E.....Columbia University.
Crawford, Albert C.....Bureau of Animal Industry, U. S. Dept. of Agriculture.
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Dunham, Edward K.....New York University.
Duval, Charles W.....Tulane University.

Edmunds, C. W.....University of Michigan.
Edsall, David L.....University of Pennsylavnia.
Eisenbrey, A. B.....New York University.
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Elser, William J.....Cornell University Medical College.
Emerson, Haven.....Columbia University.
Erlanger, Joseph.....University of Wisconsin.
Ewing, James.....Cornell University Medical College.

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Field, Cyrus W.....University of Louisville.
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Flexner, Simon.....Rockefeller Institute for Medical Research.
Flournoy, Thomas.....Bellevue Hospital, New York City.
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Foster, Nellis B.....Columbia University.

Gager, C. Stuart.....University of Missouri.
Gay, Frederick P.....Harvard University.
Gibson, Robert B.....University of Missouri.
Gies, William J.....Columbia University.
Glaser, Otto C.....University of Michigan.
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HERTER, CHRISTIAN A. ..... Columbia University.
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MacLeod, J. J. R.....Western Reserve University, Cleveland.
MacNeal, Ward J.....University of Illinois.
McClendon, J. F.....Cornell University Medical College.
Mall, Franklin P.....Johns Hopkins University.
Mandel, Arthur R.....New York University.
Mandel, John A.....New York University.
Mathews, Albert P.....University of Chicago.
Maury, J. W. Draper.....Columbia University,
Mayer, Alfred.....Marine Laboratory of the Carnegie Institution. Tortugas, Fla.
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Mendel, Lafayette B.....Yale University.
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Morse, Max.....City College of New York.
Murlin, John R.....New York University.
Murphy, John B.....Northwestern University Medical School, Chicago.

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Oertel, Horst.....Sage Institute of Pathology, City Hospital, New York.
Ophüls, William.....Cooper Medical College, San Francisco.
Opie, Eugene L.....Rockefeller Institute for Medical Research.
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Ott, Isaac.....Medico-Chirurgical College, Philadelphia.

Pappenheimer, Alvin M.....Bellevue Hospital, New York City.
Park, William H.....New York University.
Parker, George H.....Harvard University.
Pearce, Richard M.....New York University.
Pearl, Raymond.....Maine Agricultural Experiment Station, Orono, Maine.
Pfaff, Franz.....Harvard University.
Porter, William T.....Harvard University.
Pratt, Joseph H.....Harvard University.

Ravenel, Mazÿck P.....University of Wisconsin.

REICHERT, EDWARD T.....University of Pennsylvania.
RICHARDS, ALFRED N....Northwestern University Medical School, Chicago.
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ROBERTSON, T. BRAILSFORD.....University of California.
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SIMPSON, SUTHERLAND.....Cornell University, Ithaca, N. Y.
SMITH, THEOBALD.....Harvard University.
SOLLMAN, TORALD.....Western Reserve University, Cleveland.
SOUTHARD, E. E.....Harvard University.
STEINHARDT, EDNA.....University of Michigan.
STEWART, GEORGE N.....Western Reserve University, Cleveland.
STEWART, HUGH A.....Columbia University.
STILES, PERCY G.....Massachusetts Institute of Technology.
STOCKARD, CHAS. R.....Cornell Medical School.
STOOKEY, LYMAN B.....University of Southern California, Los Angeles.
STOREY, THOMAS A.....City College of New York.
STRONG, RICHARD P.....U. S. Public Health and Marine-Hospital Service, Manila.
SWEET, J. EDWIN.....University of Pennsylvania.
SWIFT, H. F.....New York University.
SYMMERS, DOUGLAS.....New York Hospital.

TAYLOR, ALONZO E.....University of California.
TEAGUE, OSCAR.....U. S. Department of the Interior, Bureau of Science, Manila.
TERRY, B. T.....Rockefeller Institute for Medical Research.
TODD, JOHN L.....MacDonald College, St. Anne de Bellevue, Quebec.
TORREY, JOHN C.....Cornell University Medical College.
TYZZER, E. E.....Harvard University.

UNDERHILL, FRANK P.....Yale University.

VAN SLYKE, DONALD D.....Rockefeller Institute for Medical Research.
VAUGHAN, VICTOR C.....University of Michigan.

Wadsworth, Augustus B.....Columbia University.
Wallace George B.....New York University.
Warthin, Aldred S.....University of Michigan.
Weil, Richard.....Cornell University Medical College.
Welch, William H.....Johns Hopkins University.
Wells, H. Gideon.....University of Chicago.
Williams, Anna W.....Department of Health, New York City.
Williams, Herbert U.....University of Buffalo.
Wilson, Edmund B.....Columbia University.
Wolbach, S. Burt.....Cornell University Medical College.
Wolf, Charles G. L.....Cornell University Medical College.
Wood, Francis C.....Columbia University
Woodruff, Lorande Loss.....Yale University.

Yatsu, Naohidé.....University of Japan.
Yerkes, Robert M.....Harvard University.

Zinsser, Hans.....Columbia University.

Total number of members at the close of the academic year, 1909–'10 : **205.**

OFFICERS.[1]

1903–1910.

	1903–'04	1904–'05	1905–'06	1906–'07
President	Meltzer	Meltzer	Wilson	Flexner
Vice-President	Park	Ewing	Dunham	Dunham
Librarian	Lusk	Lusk	Lusk	———
Treasurer	Calkins	Calkins	Calkins	Calkins
Secretary	Gies	Gies	Gies	Gies

	1907–'08	1908–'09	1909–'10	1910–'11
President	Flexner	Lee	Lee	Morgan
Vice-President	Morgan	Morgan	Gies	Gies
Treasurer	Calkins	Lusk	Lusk	Lusk
Secretary	Gies	Gies	Opie	Opie

[1]Council—The Past Presidents and the Officers.

CLASSIFIED LIST OF MEMBERS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE.

Resident (Greater New York).

Bellevue Hospital.—Thomas Flournoy, Charles Norris, Alwin M. Pappenheimer.

Columbia University.—Stanley R. Benedict, Russell Burton-Opitz, Gary N. Calkins, Henry E. Crampton, Richard H. Cunningham, Haven Emerson, Nellis B. Foster, William J. Gies, Christian A. Herter, Philip H. Hiss, Theodore C. Janeway, Frederic S. Lee, Isaac Levin, W. G. MacCallum, J. W. Draper Maury, Thomas H. Morgan, Henry C. Sherman, Hugh A. Stewart, Augustus B. Wadsworth, Edmund B. Wilson, Francis C. Wood, Hans Zinsser.

Cornell University Medical College.—S. P. Beebe, B. H. Buxton, William J. Elser, James Ewing, Robert A. Hatcher, Graham Lusk, J. F. McClendon, A. I. Ringer, Philip A. Shaffer, Chas. R. Stockard, John C. Torrey, Richard Weil, C. G. L. Wolf.

Mt. Sinai Hospital.—Charles A. Elsberg.

New York City College.—A. J. Goldfarb, Max Morse, Thomas A. Storey.

New York City Departments. Education.—C. Ward Crampton. *Health.*—James P. Atkinson, Edwin J. Banzhaf, L. W. Famulener, Alfred F. Hess, Anna W. Williams.

New York Hospital.—Douglas Symmers.

New York Polyclinic Medical School.—Isaac Adler.

New York Post-Graduate Medical School.—Ludwig Kast.

New York University.—Harlow Brooks, J. V. Cooke, Edward K. Dunham, A. B. Eisenbrey, Holmes C. Jackson, Arthur R. Mandel, John A. Mandel, John R. Murlin, William H. Park, Richard M. Pearce, H. D. Senior, H. F. Swift, George B. Wallace.

Pathological Institute, Wards Island.—Adolph Meyer.

Rockefeller Institute for Medical Research.—John Auer, Alexis Carrel, R. I. Cole, A. R. Dochez, Simon Flexner, Walter A. Jacobs, Don R. Joseph, Richard V. Lamar, P. A. Levene, Paul A. Lewis, Jacques Loeb, S. J. Meltzer, Gustave M. Meyer, Hideyo Noguchi, Eugene L. Opie, Peyton Rous, B. T. Terry, Donald D. Van Slyke.

Sage Institute of Pathology, City Hospital.—Horst Oertel.

St. Francis Hospital.—Fritz Schwyzer.

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819 Madison Avenue.—H. D. Dakin.

449 E. 57th Street.—Isaac F. Harris.

Non-Resident.

Baltimore Medical College.—Charles E. Simon.

Carnegie Institution of Washington.—Francis G. Benedict (*Nutrition Laboratory, Boston*), Charles B. Davenport (*Station for Experimental Evolution, Cold Spring Harbor, N. Y.*), D. T. MacDougal (*Washington*), Alfred G. Mayer (*Marine Laboratory, Tortugas, Fla.*).

Connecticut Agricultural Experiment Station (*New Haven*).—Thomas B. Osborne.

Cooper Medical College (*San Francisco*).—William Ophüls.

Georgia State Board of Health (*Atlanta*).—Katharine R. Collins.

Maine Agricultural Experiment Station (*Orono*).—Raymond Pearl.

Massachusetts Institute of Technology.—Percy G. Stiles.

Medico-Chirurgical College (*Philadelphia*).—Isaac Ott.

Michael Reese Hospital (*Chicago*).—James W. Jobling.

Northwestern University Medical School (*Chicago*).—J. B. Murphy, Alfred N. Richards.

Philippine Medical School (*Manila*).—A. O. Shaklee.

Oakland College of Medicine.—Martin H. Fischer.

U. S. Departments. Agriculture (Washington, D. C.).—Carl L. Alsberg, William N. Berg, Albert C. Crawford, William Salant; *Interior* (Philippine Islands, Bureau of Science, Manila).—Richard P. Strong, Oscar Teague. *Treasury* (Public Health and Marine-Hospital Service).—Walter R. Brinckerhoff, Honolulu, Hawaii; John F. Anderson, Wm. H. Hale, Reid Hunt, Joseph H. Kastle and W. H. Schultz, Washington, D. C.

Universities. Buffalo.—G. H. A. Clowes, Herbert U. Williams. *California.*—T. Brailsford Robertson, Alonzo E. Taylor. *Chicago.*—R. R. Bensley, A. J. Carlson, Ludvig Hektoen, Edwin O. Jordan, Waldemar Koch, Frank R. Lillie, Albert P. Mathews, H. Gideon Wells. *Cornell.*—Andrew Hunter, Sutherand Simpson. *Harvard.*—Herman M. Adler, Walter B. Cannon, W. T. Councilman, Otto Folin, Frederick P. Gay, G. H. Parker, Franz Pfaff, W. T. Porter, Joseph H. Pratt, M. J. Rosenau, Theobald Smith, E. E. Southard, E. E. Tyzzer, Robert M. Yerkes. *Illinois.*—Philip B. Hawk, Ward J. MacNeal. *Japan.*—Naohidé Yatsu. *Johns Hopkins.*—John J. Abel, Rufus I. Cole, Harvey W. Cushing, W. W. Ford, W. S. Halsted, William H. Howell, H. S. Jennings, Walter Jones, F. P. Mall, William H. Welch. *Louisville.*—Cyrus W. Field. *MacDonald College* (Ste. Anne de Bellevue, Quebec).—John L. Todd. *McGill* (Montreal).—J. George Adami, S. Burt Wolbach. *Michigan.*—C. W. Edmunds, Otto C. Glaser, A. W. Hewlett, Carl G. Huber, Warren P. Lombard, Frederick G. Novy, Edna Steinhardt, Victor C. Vaughan, Aldred S. Warthin. *Missouri.*—C. Stuart Gager, Robert B. Gibson. *Pennsylvania.*—Alexander C. Abbott, David L. Edsall, Ralph S. Lillie, Leo Loeb, Edward T. Reichert, J. Edwin Sweet. *Pittsburgh.*—C. C. Guthrie, Oskar Klotz. *Princeton.*—Edwin G. Conklin. *Southern California* (Los Angeles).—Lyman B. Stookey. *St. Louis.*—E. P. Lyon. *Toronto.*—T. G. Brodie, J. B. Leathes, A. B. Macal-

lum. *Tulane.*—Charles W. Duval. *Wisconsin.*—Charles R. Bardeen, C. H. Bunting, Joseph Erlanger, Arthur S. Loevenhart, Mazÿck P. Ravenel. *Western Reserve* (Cleveland).—George W. Crile, J. J. R. Macleod, Torald Sollmann, G. N. Stewart. *Yale.*—R. H. Chittenden, L. J. Cole, Ross G. Harrison, Yandell Henderson, Lafayette B. Mendel, Frank P. Underhill, Lorande Loss Woodruff.

University College (London).—Arthur R. Cushny.

Wistar Institute of Anatomy (Philadelphia).—H. H. Donaldson, Shinkishi Hatai.

INDEX

OF THE

SCIENTIFIC PROCEEDINGS.

[THE NUMERALS IN THIS INDEX CORRESPOND WITH THE NUMERALS IN PARENTHESIS ABOVE THE TITLES OF THE ABSTRACTS. PAGES ARE NOT INDICATED.]

Adrenalin, 459; in phlorizin diabetes, 415.
Adsorption of venom, 467.
Alcohol, influence on developing embryos of, 411.
Alkali in the development of the egg of the sea urchin, 484.
Amino-nitrogen as a measure of proteolysis, 522; determination of, 439.
Ammonia destroying power of the liver, 442; tetany, 487.
Amyl acetate, toxicity of, 508; nitrite and venous blood flow, 451.
Anaphylactic death, 429; "shock," 430, 431.
Anaphylaxis, 474.
Anastomosed blood vessels, structure of, 505.
Anemia, effect on goitre of, 438.
Anesthetics, 411.
Antibodies in cancer, 418.
Antibody, syphilitic, 421.
Antienzymes of the blood serum, 472.
Antiferments and ferments, 447.
Antitoxin, diphtheria, 504.
Antitrypsin, 500.
Aorta, temporary diversion from the ventricle to, 457.
Aphids, chromosomes in eggs of 513.
Arterial lesions in the dog, experimental, 515; lesions in the rabbit, spontaneous, 477; wall, compression of, 510.
Artificial respiration and strychnin, 470.
Autodermic skin grafts, 464.
Autolysis, 414.
Autolyzed tissue, resistance to the growth of cancer induced by, 448.

Bacteria, elimination of, 460.
Bacterial infections, conglutination reaction with, 424.
Barium and magnesium, antagonistic action of, 428.
Bile, caffein in, 509.
Bleeding experiments, 524.
Blood, distribution in shock of, 498; elimination of bacteria from, 460; pressure, relation to thalamus of, 516.
Blood-vessels, anastomosed, 505.
Brain, sulphur compounds in, 413.

Caffein, elimination of, 509.
Calcium and sodium, antagonistic action of, 449; excretion after parathyroidectomy of, 419.
Cancer, antibodies in 418; hemolysis in, 463; immunity to, 476; resistance to the growth of, 448; skin grafts in 464.
Cardio-inhibitory nerves, 435.
Cataphoresis of proteids, 479.
Central nervous system, influence on inflammation of, 525.

[THE NUMERALS CORRESPOND WITH THOSE ABOVE THE ASBTRACTS.]

Cerebro-medullary circulation, 482.
Chloroform, administration of, 511.
Chromosomes in parthenogenetic and sexual eggs, 513.
Ciliary and muscular movements, 423.
Cirrhosis of the liver, experimental, 445.
Collodian sacs, filtration through, 490.
Complement fixation, non-specific, 444; non-fixation of, 420.
Compression of the arterial wall, 510.
Conglutination reaction, 424.
Conjugation, reproduction without, 501
Curarin and strychnin, 470.
Cyclopia, artificial, 478.

Depressor action of urine, 459.
Diphtheria antitoxin, precipitation of, 504.
Drosophila, hybridization in, 512.
Duodenum, peristalsis of, 469.

Egg, development of, 485; of the sea urchin, development of, 484.
Embryo, transplanted, 453.
Embryonic tissue implanted in the mother, 452.
Embryos, influence of alcohol on, 411; without nerves, 507.
Energy metabolism, 422.
Engrafted tissue, 436, 437.
Enzymes, intracellular proteolytic, 471; of the blood serum, 472.
Erythrocytes, resistance in disease of, 412.
Ether, administration of, 511.

Ferments and antiferments, 447.
Foreign bodies and uterine mucosa, 466.
Fröhlich's theory of the treppe, 494.

Gas tension in fluids, 523.
Gastric secretion and glycerin, 432.
Glucosamin, non-production of sugar from, 493.
Glycerin and gastric secretion, 432.
Glycosuria, production of, 440.
Goitre, hyperplastic, 438.
Grave's disease, neuropsychologic changes in, 462.

Heart in embryos without nerves, 507.
Heloderma suspectum, venom of, 467.
Hemolysins, 412.
Hemolysis in cancer, 463.
Hybridization in Drosophila, 512.
Hydrophobic blood serum, vaso-reaction with, 503.
Hyperemia, effect on goitre of, 438.

Immune bodies with organ transplantation, 486.
Immunity to cancer, 476.
Inflammation, influence of central nervous system on, 525.
Infundibular extract of the pituitary, glycosuria with, 440.
Inheritance of plumage color, 518.
Innervation, voluntary, 489.
Insufflation method, 470.
Intestine, elimination of bacteria through, 460.
Intratracheal insufflation, 426.
Iodin in organic material, 416.
Irritability of muscle, 449.
Isodermic skin grafts, 464.

Karyokinetic figure, 492.
Kidneys, transplantation of, 456.
Krogh's microtonometer, 523.

Lecithin, influence on protein metabolism of, 517.
Liquefying bacteria, detection of, 519.
Liver, enzymes with degenerative

[THE NUMERALS CORRESPOND WITH THOSE ABOVE THE ABSTRACTS.]

changes in, 472; intracellular proteolytic enzymes of, 471.

Magnesium and barium, antagonistic action of, 428; excretion after parathyroidectomy of, 419; inhibitory effect of, 449; 469; salts, 434; 435.
Mammary glands, nucleoprotein of, 425.
Membrane formation, 485.
Microtonometer, Krogh's, 523.
Morbus ceruleus, 480.
Motor nerve impulses, 434; nerves, 435.
Muscle, contraction of, 489.
Muscular and ciliary movements, 423.
Mutation period in Drosophila, 512.

Neuropsychologic changes, 462.
Nitrogen, elimination in the pregnant dog, 488; metabolism, 480.
Nucleic acid of yeast, 465.
Nucleoprotein of the mammary glands, 425.

Oils, influence on protein metabolism of, 517.
Ovarian tissue, engrafted, 436.
Oxidations of tissue *in vitro,* 506.

Pancreatic extract, activation of, 491; glycosuria with, 440.
Parabiosis, 418; 468.
Paramecium, reproduction of, 501.
Parathryoid extract, glycosuria with, 440.
Parathyroidectomy, 419.
Parenteral protein assimilation, 481.
Parturient women, energy metabolism of, 422.
Pepsin, clinical estimation of, 496.
Peristalsis, effect of magnesium upon, 469.
Phlorizin, 493; in diabetes, 415.
Phototaxis, rhythm in, 502.
Phyloxerans, chromosomes in eggs of, 513.
Physico-chemical methods for the study of autolysis, 414.
Pituitary and thyroid glands, 417.
Plumage color, inheritance of, 518.
Pneumonia, experimental lobar, 473.
Poliomyelitis, experimental, 441.
Precipitin reaction, 421.
Precipitins and diphtheria antitoxin, 504.
Pregnant dog, nitrogen elimination in, 488.
Proteids, cataphoresis of, 479.
Protein assimilation, parenteral, 481; metabolism, 517; specific dynamic action of, 495.
Proteins, analysis of, 521; unbroken, 454.
Proteolysis and amino-nitrogen, 522.
Protozoa, shaking experiments with, 446.
Ptyalin in relation to diet, 443.
Purines, metabolism of, 497.

Renal tissue, engrafted, 437.
Replantation of the spleen, 458.
Reproduction without conjugation, 501.
Respiration, by intratracheal insufflation, 426; relation to thalamus of, 516.

Salivary secretion, rate of, 443.
Sensitization with tuberculin, 455.
Sensory nerves, 435; stimulation, 434.
Sertoli cells, 514.
Shaking experiments with protozoa, 446.
Shock, conditions of surgical, 499; distribution of blood in, 498; neuropsychologic changes in, 462.

[THE NUMERALS CORRESPOND WITH THOSE ABOVE THE ABSTRACTS.]

Sodium and calcium, antagonistic action of, 449; salts, influence on chemical stimulation of, 520.
Spleen, blood supply of, 516; replantation of, 458.
Starch-dextrin reaction, 483.
Stimulation, nature of chemical, 520.
Stomach, peristalsis of, 469; vaso-motor nerves of, 450.
Strychnin, recovery from, 470.
Sugar from tyrosin and glucosamin, 493.
Sulphur compounds in brain tissue, 413, metabolism, 480.
Summation of stimuli, 433.
Syphilis, resistance of erythrocytes, with, 412.
Syphilitic antibody, 421.

Tabardillo, 461.
Testicular tissue, engrafted, 436.
Tetany, ammonia, 487.
Thalamus, relation to respiration and blood pressure of, 516.
Thoracic organs, operation upon, 427.
Thyroid and pituitary glands, 417; tissue, engrafted, 437; parathyroidectomy, 442.
Transplantation of kidney, 456; of organs, 486.
Transplanted tumor and embryo, 453.
Treppe, 494.
Tubercle bacillus, vaso-motor reaction produced by extracts of, 475.
Tuberculin, sensitization with, 455.
Tumor, transplanted, 453.
Typhus fever, Mexican, 461.
Tyrosin, non-production of sugar from, 493.

Urine, depressor action of, 459.
Uterine mucosa and foreign bodies, 466.

Vagus, resection with anaphylaxis of, 474.
Vaso-motor nerves of the stomach, 450.
Vaso-reaction in dogs, 503; produced by extracts of tubercle bacillus, 475.
Vaughan's split products, 454.
Venom, adsorption of, 467.
Venous blood flow and amyl nitrite, 451.
Ventricle, temporary diversion to aorta from, 457.

Yeast, nucleic acid of, 465.

PROCEEDINGS

OF THE

SOCIETY FOR

EXPERIMENTAL BIOLOGY AND MEDICINE

THIRTY FIFTH MEETING

COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY

NEW YORK CITY

OCTOBER 20, 1909

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CONTENTS.

CHARLES R. STOCKARD: The influence of alcohol and other anesthetics on developing embryos. 1 (411).

RICHARD WEIL: On the variation in the resistance of human erythrocytes in disease to hemolysins, with especial reference to syphilis. 2 (412).

W. KOCH and F. W. UPSON: The distribution of sulphur compounds in brain tissue. 3 (413).

ROBERT L. BENSON and H. GIDEON WELLS: The study of autolysis by physico-chemical methods. 4 (414).

A. I. RINGER (By invitation): Influence of adrenalin in phlorhizin diabetes. 5 (415).

ANDREW HUNTER: A method for the determination of small quantities of iodine in organic material. 6 (416).

SUTHERLAND SIMPSON and ANDREW HUNTER: Relations between the thyroid and pituitary glands. 7 (417).

PEYTON ROUS: Parabiosis as a test for circulating antibodies in cancer. 8 (418).

JEAN V. COOKE (By invitation): The excretion of calcium and magnesium after parathyroidectomy. 9 (419).

HIDEYO NOGUCHI: Non-fixation of complement. 10 (420).

HIDEYO NOGUCHI: The fate of so-called syphilitic antibody in the precipitin reaction. 11 (421).

THORNE M. CARPENTER and JOHN R. MURLIN: The energy metabolism of parturient women. 12 (422).

ALFRED G. MAYER: The relation between ciliary and muscular movements. 13 (423).

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EXPERIMENTAL BIOLOGY AND MEDICINE

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THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

NEW YORK CITY

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1910

CONTENTS.

FREDERICK P. GAY and WILLIAM P. LUCAS : The value of the conglutination reaction as a means of diagnosis of acute bacterial infections. 14 (424).
J. A. MANDEL : Analysis of the cleavage products of the nucleoprotein of the mammary glands. 15 (425).
S. J. MELTZER and J. AUER : Respiration by continuous intra-tracheal insufflation of air. A demonstration. 16 (426).
ALEXIS CARREL : Demonstration of animals whose thoracic organs have been operated upon. 17 (427).
DON R. JOSEPH and S. J. MELTZER : The mutual antagonistic life-saving action of barium and magnesium. A demonstration. 18 (428).
J. AUER and P. A. LEWIS : A demonstration of the cause of acute anaphylactic death in guinea pigs. 19 (429).
RICHARD M. PEARCE and A. B. EISENBREY : Anaphylactic "shock" in the dog. 20 (430).
JOHN F. ANDERSON and W. H. SCHULTZ : The cause of serum anaphylactic shock and some methods of alleviating it. 21 (431).
L. KAST : The influence of glycerin on gastric secretion. 22 (432).
FREDERIC S. LEE and MAX MORSE : The summation of stimuli. 23 (433).
A. H. RYAN and F. V. and C. C. GUTHRIE : The action of magnesium salts : A. In relation to motor nerve impulses ; B. In relation to sensory stimulation. 24 (434).
C. C. and F. V. GUTHRIE and A. H. RYAN : The effects of direct application of magnesium salts : A. To motor and sensory nerves ; B. To cardio-inhibitory nerves. 25 (435).
C. C. GUTHRIE : The survival and growth of subcutaneously engrafted ovarian and testicular tissue. 26 (436).
C. C. GUTHRIE : The survival of engrafted thyroid and renal tissue. 27 (437).
C. C. GUTHRIE : The effect of anemia and of double hyperemia on hyperplastic goitre. 28 (438).
DONALD D. VAN SLYKE : A method for the determination of amino-nitrogen and its applications. 29 (439).
ISAAC OTT and JOHN C. SCOTT : Note on the production of glycosuria by parathyroids, pancreas and the infundibular extract of the pituitary. 30 (440).
SIMON FLEXNER and PAUL A. LEWIS : A report on experimental poliomyelitis. 31 (441).
A. J. CARLSON and CLARA JACOBSON : The depression of the ammonia destroying power of the liver after thyroid-parathyroidectomy. 32 (442).
A. J. CARLSON and A. L. CRITTENDEN : The relation of ptyalin concentration to the diet and to the rate of salivary secretion. 33 (443).
HIDEYO NOGUCHI : On non-specific complement fixation. 34 (444).
EUGENE L. OPIE : Experimental cirrhosis of the liver. 35 (445).
MAX MORSE : Shaking experiments with protozoa. 36 (446).

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Auer, Ewing, Famulener, Foster, Gies, Harris, Hatcher, Hunter, Joseph, Lamar, Lee, Levene, Levin, Meltzer, Mayer, Meyer, Morgan, Morse, Murlin, Norris, Noguchi, Opie, Park, Pearce, Rous, Symmers, Schaffer, Stockard, Van Slyke, Wadsworth, Weil, Wolf, Zinsser.

Dates of the next two regular meetings:

December 15, 1909. February 16, 1910.

PROCEEDINGS

OF THE

SOCIETY FOR

EXPERIMENTAL BIOLOGY AND MEDICINE

THIRTY SEVENTH MEETING

PHYSIOLOGICAL LABORATORY, NEW YORK UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE

NEW YORK CITY

FEBRUARY 16, 1910

VOLUME VII

No. 3

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1910

CONTENTS.

R. Weil and S. Feldstein : A new method for testing the interaction of ferments and anti-ferments. 37 (447).

Isaac Levin : Resistance to the growth of cancer induced in rats by injection of autolyzed rat tissue. 38 (448).

Don R. Joseph and S. J. Meltzer : The inhibitory effect of magnesium upon indirect and direct irritability of frog muscle and the antagonistic action of sodium and calcium upon this effect. 39 (449).

R. Burton-Opitz : On the vaso-motor nerves of the stomach. 40 (450).

R. Burton-Opitz and H. F. Wolf : The change in the venous bloodflow on administration of amyl nitrite. 41 (451).

Peyton Rous : The fate of embryonic tissue implanted in the mother. 42 (452).

Peyton Rous : The behavior of transplanted mixtures of tumor and embryo. 43 (453).

Edwin J. Banzhaf and Edna Steinhardt : Vaughan's split products and unbroken proteins. A comparative study of their effects. 44 (454).

J. P. Atkinson and C. B. Fitzpatrick : Notes on sensitization with tuberculin to tubercular rabbit-serum. 45 (455).

Alexis Carrel : Remote results of the replantation of the kidneys. 46 (456).

Alexis Carrel : Temporary diversion from the left ventricle to the descending aorta. 47 (457).

Alexis Carrel : Remote results of the replantation of the spleen. 48 (458).

Richard M. Pearce and Arthur B. Eisenbrey : The mechanism of the depressor action of dog's urine with some observations on the antagonistic action of adrenalin. 49 (459).

Alfred F. Hess : On the elimination of bacteria from the blood through the wall of the intestine. 50 (460).

John F. Anderson and Joseph Goldberger : A report on the production of tabardillo, or Mexican typhus fever, in monkeys. 51 (461).

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THIRTY EIGHTH MEETING

CORNELL UNIVERSITY MEDICAL COLLEGE

NEW YORK CITY

APRIL 20, 1910

VOLUME VII

No. 4

NEW YORK

1910

CONTENTS.

GEORGE W. CRILE: On the neurocytologic changes in shock, infection, Graves' disease, and certain drugs, with a note on fear in rabbits. 52 (**462**).

GEORGE W. CRILE: Further observations on hemolysis in cancer. 53 (**463**).

GEORGE W. CRILE: On the behavior of autodermic and isodermic skin grafts in cancer. 54 (**464**).

P. A. LEVENE and W. A. JACOBS: On yeast nucleic acid. 55 (**465**).

LEO LOEB: The reaction of the uterine mucosa towards foreign bodies introduced into the uterine cavity. 56 (**466**).

LEO LOEB and MOYER S. FLEISHER: The adsorption of the venom of Heloderma suspectum. 57 (**467**)

R. A. LAMBERT (By invitation): A note on the parabiosis of rats and mice. 58 (**468**).

DON R. JOSEPH and S. J. MELTZER: A demonstration of the inhibitory effect of magnesium upon normal and artificial peristalsis of the stomach and duodenum. 59 (**469**).

A. O. SHAKLEE and S. J. MELTZER: Recovery from fatal doses of strychnin by the aid of curarin and artificial respiration (insufflation method). 60 (**470**).

A. R. DOCHEZ: Intracellular proteolytic enzymes of liver. 61 (**471**).

EUGENE L. OPIE and BERTHA I. BARKER: Enzymes and antienzymes of the blood serum with certain degenerative changes in the liver. 62 (**472**).

R. V. LAMAR and S. J. MELTZER: A preliminary note upon experimental lobar pneumonia with a demonstration of specimens. 63 (**473**).

JOHN AUER: The effects of resection of one vagus upon serum anaphylaxis in guinea-pigs. 64 (**474**)

J. P. ATKINSON and CHARLES B. FITZPATRICK: Notes on the vaso-reaction in dogs produced by injections of extracts of the tubercle bacillus. 65 (**475**).

ISAAC LEVIN: Immunity to the growth of cancer induced in rats by treatment with mouse tissue. 66 (**476**).

ISAAC LEVIN and JOHN H. LARKIN: The early stages of the spontaneous arterial lesions in the rabbit. 67 (**477**).

J. F. MCCLENDON: Artificial cyclopia in the smelt. 68 (**478**).

J. F. MCCLENDON: Cataphoresis of proteids in the living cell. 69 (**479**).

N. B. FOSTER: Nitrogen and sulphur metabolism in morbus ceruleus. 70 (**480**).

P. A. LEVENE and G. M. MEYER: On parenteral protein assimilation. 71 (**481**).

ARTHUR BRADLEY EISENBREY: A method of isolating the cerebro-medullary circulation. 72 (**482**).

EDWARD TYSON REICHERT: A reversion of the starch-dextrin reaction. 73 (**483**).

JACQUES LOEB: The rôle of alkali in the development of the egg of the sea-urchin. 74 (**484**).

JACQUES LOEB: How can the process underlying membrane formation cause the development of the egg? 75 (**485**).

ARNO B. LUCKHARDT: A study of the origin of the immune bodies by the method of organ transplantation. 76 (**486**).

CLARA JACOBSON (By invitation): The concentration of ammonia in the blood of dogs and cats necessary to produce ammonia tetany. 77 (**487**).

J. R. MURLIN: The daily curve of nitrogen elimination in the pregnant, as compared with the non-pregnant dog. 78 (**488**).

HORATIO B. WILLIAMS (By invitation): Contraction of muscle during voluntary innervation. 79 (**489**).

EDNA STEINHARDT: Filtration through collodion sacs. 80 (**490**).

A. R. DOCHEZ: The activation of pancreatic extract. 81 (**491**).

T. H. MORGAN: Experiments bearing on the nature of the karyokinetic figure. 82 (**492**).

A. I. RINGER and GRAHAM LUSK: The non-production of sugar from tyrosin and glucosamin in phlorizin glycosuria. 83 (**493**).

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THIRTY NINTH MEETING

SHEFFIELD BIOLOGICAL LABORATORY
YALE UNIVERSITY

NEW HAVEN

MAY 18, 1910

VOLUME VII

No. 5

NEW YORK

1910

CONTENTS.

Biography of Frederic Schiller Lee.

FREDERIC S. LEE and E. N. HARVEY: An examination of Fröhlich's theory of the treppe. 84 (494).

GRAHAM LUSK: An attempt to discover the cause of the specific dynamic action of protein. 85 (495).

WILLIAM C. ROSE (by invitation): A modified method for the clinical estimation of pepsin. 86 (496).

LAFAYETTE B. MENDEL and JOHN F. LYMAN: The metabolism of the purines in man. 87 (497).

E. P. LYON and J. L. SWARTS: The distribution of blood in shock. 88 (498).

VANDELL HENDERSON: The fundamental conditions of surgical shock. 89 (499).

R. WEIL and S. FELDSTEIN: Observations on the nature of the antitrypsin of the serum. 90 (500).

LORANDE LOSS WOODRUFF: On the power of reproduction without conjugation in Paramecium. 91 (501).

MAX WITHROW MORSE: Alleged rhythm in phototaxis synchronous with ocean tides. 92 (502).

J. P. ATKINSON and C. B. FITZPATRICK: The vaso reaction of hydrophobic rabbit's blood serum in dogs. 93 (503).

J. P. ATKINSON and E. J. BANZHAF: The precipitation of diphtheria antitoxin by means of precipitins. 94 (504).

C. C. GUTHRIE: Further observations on the structure of anastomosed blood vessels. 95 (505).

F. V. GUTHRIE (by invitation): Modification of tissue oxidations *in vitro*. 96 (506).

DAVENPORT HOOKER (by invitation): The development and function of the heart in embyros without nerves. 97 (507).

WILLIAM SALANT: The toxicity of amyl acetate. 98 (508).

WILLIAM SALANT and W. O. EMERY: The elimination of caffein in the bile. 99 (509).

THEODORE C. JANEWAY and EDWARDS A. PARK: An experimental study of the resistance to compression of the arterial wall. 100 (510).

A. O. SHAKLEE: A simple device for regulating the administration of ether or chloroform, with either artificial or voluntary respiration. 101 (511).

T. H. MORGAN: Hybridization in a mutating period in Drosophila. 102 (512).

T. H. MORGAN: The chromosomes in the parthenogenetic and sexual eggs of phylloxerans and aphids. 103 (513).

F. M. HANES (by invitation): The biological significance of the Sertoli cells. 104 (514).

ISAAC LEVIN and JOHN R. LARKIN: Studies on experimental arterial lesions in the dog. 105 (515).

E. SACHS (by invitation): The relation of the thalamus to respiration, blood pressure and blood supply of the spleen. 106 (516).

LLOYD H. MILLS and JOHN R. MURLIN: The influence of oils and of lecithin on the protein metabolism. 107 (517).

C. B. DAVENPORT: Inheritance of plumage color in poultry. 108 (518).

JOHN C. TORREY: A new and comparatively rapid method for the detection of liquefying bacteria. 109 (519).

RALPH S. LILLIE: On the nature of chemical stimulation and on the influence of neutral sodium salts on various forms of chemical stimulation. 110 (520).

DONALD D. VAN SLYKE: A new method for the analysis of proteins. 111 (521).

DONALD D. VAN SLYKE: The determination of amino nitrogen as a measure of the rate and extent of proteolysis. 112 (522).

M. M. SCARBROUGH (by invitation): A demonstration of Krogh's microtonometer for the determination of gas tensions in fluids. 113 (523).

H. B. GOODALE (by invitation): Breeding experiments in poultry. 114 (524).

W. G. MACCALLUM: Inflammation in tissues separated from connection with the central nervous system. 115 (525).

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Sage Institute of Pathology, City Hospital.—Horst Oertel.

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Maine Agricultural Experiment Station (*Orono*).—Raymond Pearl.

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Oakland College of Medicine.—Martin H. Fischer.

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University College (London).—Arthur R. Cushny.

Wistar Institute of Anatomy (Philadelphia).—H. H. Donaldson, Shinkishi Hatai.

Members present at the thirty seventh meeting:

Atkinson, Auer, Banzhaf, Cole, R. I., Flexner, Gies, Hiss, Jackson, Joseph, Lee, Levin, Lusk, Mandel, A. R., MacCallum, McClendon, Meltzer, Morgan, Moss, Opie, Park, Rous, Shaklee, Stockard, Van Slyke, Wallace, Weil.

Members elected at the thirty seventh meeting:

J. V. Cooke, A. R. Dochez, J. B. Leathes.

Dates of the next two regular meetings:

April 20, 1910. May 18, 1910.

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